Clinical trial results:
Dose response study of Patient Controlled Analgesia (PCA) of S-ketamine in orthopaedic spine surgery patients

Summary

EudraCT number	2016-002887-14
Trial protocol	FI
Global end of trial date	01 March 2020

Results information

Result version number	v1 (current)
This version publication date	25 October 2020
First version publication date	25 October 2020

Trial information

Trial identification

Sponsor protocol code	2.0

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	University of Turku
Sponsor organisation address	Kiinamyllynkatu 4-8, Turku, Finland,
Public contact	Turku Clinical Research Centre, Turku University Hospital, turkucrc@tyks.fi
Scientific contact	Turku Clinical Research Centre, Turku University Hospital, turkucrc@tyks.fi

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 September 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	31 October 2019
Global end of trial reached?	Yes
Global end of trial date	01 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

This randomized, double-blinded, controlled study is aimed to study the dose-response using combining adjunct S-ketamine with oxycodone in intravenous PCA bolus dosing in patients scheduled for posterolateral lumbar spine fusion with bilateral transpedicular screw instrumentation.

Protection of trial subjects:

Normal in-house operating theater routines

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 June 2015
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	Finland: 107
Worldwide total number of subjects	107
EEA total number of subjects	107

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)	89
From 65 to 84 years	18
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

One hundred and seven adult patients scheduled for elective posterolateral lumbar spine fusion with bilateral transpedicular screw instrumentation under general anesthesia were recruited between February 2017 and October 2019 of of 231 eligible patients

Pre-assignment

Screening details:

Patients were pre-screened by a preoperative care nurse, and the potentially eligible subjects were directed to investigators for further screening and information.

Period 1

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

Blinding implementation details:

An independent statistician created a computer-generated randomization list that was sent to the local hospital pharmacies, which took care of assignment. The pharmacy delivered coded PCA reservoirs with no other markings to the operation room on the day of each surgery to ensure double-blinding. Patients, researchers, and clinical staff were blinded to group allocation.

Arms

Are arms mutually exclusive?	Yes
Arm title	G1: Placebo arm

Arm description:

G1, oxycodone 1 mg ml-1 alone. The starting dose of (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) in the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Arm type	Placebo
Investigational medicinal product name	oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone.

Arm title	G2: S-Ketamine 0.25 mg/ml group

Arm description:

G2, oxycodone 1 mg ml-1 with 0.25 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Arm type	Active comparator

Investigational medicinal product name	oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone.

Investigational medicinal product name	S-ketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone - 0.25 mg/ml S-ketamine (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland; Ketanest-S 5 mg ml-1, Pfizer Manufacturing Belgium NV, Puurs, Belgium)) in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Arm title	G3: S-ketamine, 0.5 mg/ml

Arm description:

G3, oxycodone 1 mg ml-1 with 0.5 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Arm type	Active comparator
Investigational medicinal product name	oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) with S-ketamine in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone.

Investigational medicinal product name	S-ketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone - 0.5 mg/ml S-ketamine (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland; Ketanest-S 5 mg ml-1, Pfizer Manufacturing Belgium NV, Puurs, Belgium)) in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Arm title	G4: S-ketamine, 0.5 mg/ml

Arm description:

G4, oxycodone 1 mg ml-1 with 0.75 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Arm type	Active comparator
Investigational medicinal product name	oxycodone
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) with S-ketamine in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone.

Investigational medicinal product name	S-ketamine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

The starting dose of oxycodone - 0.75 mg/ml S-ketamine (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland; Ketanest-S 5 mg ml-1, Pfizer Manufacturing Belgium NV, Puurs, Belgium)) in the PCA solution was 2 mg, and the lockout interval was five minutes. When NRS was 4 or lower, the PCA oxycodone dose was decreased to 1 mg oxycodone. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Number of subjects in period 1	G1: Placebo arm	G2: S-Ketamine 0.25 mg/ml group	G3: S-ketamine, 0.5 mg/ml
Started	25	27	26
Clinical phase ended	25	26	25
Completed	25	25	25
Not completed	0	2	1
Consent withdrawn by subject	-	-	1
operation postponed	-	1	-
Lost to follow-up	-	1	-
Operation cancelled	-	-	-
Operation changed	-	-	-

Number of subjects in period 1	G4: S-ketamine, 0.5 mg/ml
Started	29
Clinical phase ended	26
Completed	25
Not completed	4
Consent withdrawn by subject	1
operation postponed	-
Lost to follow-up	1
Operation cancelled	1
Operation changed	1

Baseline characteristics

Reporting groups

Reporting group title	Study clinical phase

Reporting group description: -

Reporting group values	Study clinical phase	Total	
Number of subjects	107	107	
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	60		
full range (min-max)	28 to 78	-	
Gender categorical Units: Subjects			
Female	49	49	
Male	58	58	
Ethnic group Units: Subjects			
caucasian	107	107	

End points

End points reporting groups

Reporting group title	G1: Placebo arm

Reporting group description:

G1, oxycodone 1 mg ml-1 alone. The starting dose of (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) in the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Reporting group title	G2: S-Ketamine 0.25 mg/ml group

Reporting group description:

G2, oxycodone 1 mg ml-1 with 0.25 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Reporting group title	G3: S-ketamine, 0.5 mg/ml

Reporting group description:

G3, oxycodone 1 mg ml-1 with 0.5 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Reporting group title	G4: S-ketamine, 0.5 mg/ml

Reporting group description:

G4, oxycodone 1 mg ml-1 with 0.75 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Primary: cumulatice oxycodone consumption

End point title	cumulatice oxycodone consumption

End point description:

End point type	Primary

End point timeframe:

24 hours from the end of surgery when PCA was initiated

End point values	G1: Placebo arm	G2: S-Ketamine 0.25 mg/ml group	G3: S-ketamine, 0.5 mg/ml	G4: S-ketamine, 0.5 mg/ml
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	25	25	25	25
Units: milligram(s)/24 hours				
arithmetic mean (standard deviation)	81.9 (± 47.6)	74.1 (± 30.7)	74.7 (± 31.8)	61.3 (± 32.3)

Statistical analyses

Statistical analysis title	comparison of oxycodone consumption
Comparison groups	G1: Placebo arm v G2: S-Ketamine 0.25 mg/ml group v G3: S-ketamine, 0.5 mg/ml v G4: S-ketamine, 0.5 mg/ml
Number of subjects included in analysis	100
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Confidence interval	
level	95 %
sides	2-sided
lower limit	2.5
upper limit	97.5
Variability estimate	Standard deviation

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Follow-up (72 hours after the start of patient controlled analgesia)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	10

Reporting groups

Reporting group title	G1: Placebo arm

Reporting group description:

G1, oxycodone 1 mg ml-1 alone. The starting dose of (Oxycodone Orion 10 mg ml-1, Orion Pharma, Espoo, Finland) in the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Reporting group title	G2: S-Ketamine 0.25 mg/ml group

Reporting group description:

G2, oxycodone 1 mg ml-1 with 0.25 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Reporting group title	G3: S-ketamine, 0.5 mg/ml

Reporting group description:

G3, oxycodone 1 mg ml-1 with 0.5 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Reporting group title	G4: S-ketamine, 0.5 mg/ml

Reporting group description:

G4, oxycodone 1 mg ml-1 with 0.75 mg/ml S-ketamine. The starting dose of the patient conrolled analgesia (PCA) solution was 2 mg, and the lockout interval was five minutes. When pain (measured with numerical rating scale) was 4 or lower, the PCA oxycodone dose was decreased to 1 mg. The study-PCA dosing continued for 24 hours from the end of surgery, after which the PCA cassette was changed to only an oxycodone-containing solution (G1).

Serious adverse events	G1: Placebo arm	G2: S-Ketamine 0.25 mg/ml group	G3: S-ketamine, 0.5 mg/ml
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 25 (0.00%)	0 / 25 (0.00%)	0 / 25 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0

Serious adverse events	G4: S-ketamine, 0.5 mg/ml		
Total subjects affected by serious adverse events			

subjects affected / exposed	0 / 25 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	G1: Placebo arm	G2: S-Ketamine 0.25 mg/ml group	G3: S-ketamine, 0.5 mg/ml
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 25 (16.00%)	7 / 25 (28.00%)	6 / 25 (24.00%)
Nervous system disorders			
Nightmare			
subjects affected / exposed	4 / 25 (16.00%)	4 / 25 (16.00%)	4 / 25 (16.00%)
occurrences (all)	4	4	4
Immune system disorders			
Pruritus			
subjects affected / exposed	4 / 25 (16.00%)	7 / 25 (28.00%)	4 / 25 (16.00%)
occurrences (all)	4	7	4
Gastrointestinal disorders			
postoperative nausea and vomiting			
alternative dictionary used: MedDRA 10			
subjects affected / exposed	4 / 25 (16.00%)	3 / 25 (12.00%)	6 / 25 (24.00%)
occurrences (all)	4	3	6

Non-serious adverse events	G4: S-ketamine, 0.5 mg/ml		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 25 (20.00%)		
Nervous system disorders			
Nightmare			
subjects affected / exposed	3 / 25 (12.00%)		
occurrences (all)	3		
Immune system disorders			
Pruritus			
subjects affected / exposed	1 / 25 (4.00%)		
occurrences (all)	1		
Gastrointestinal disorders			
postoperative nausea and vomiting			
alternative dictionary used: MedDRA 10			

subjects affected / exposed occurrences (all)	5 / 25 (20.00%) 5		

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