# 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<br>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<br>Units: years | | | |
| median | 60 | | |
| full range (min-max) | 28 to 78 | - | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 49 | 49 | |
| Male | 58 | 58 | |
| Ethnic group<br>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<br>occurrences (all) | 5 / 25 (20.00%)<br>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