# Clinical trial results:
# The effect of intravenous ketamine on the MAC of sevoflurane – a randomized, placebo controlled, double blinded clinical trial

## Summary

| | |
|---|---|
| EudraCT number | 2012-001908-38 |
| Trial protocol | AT |
| Global end of trial date | 31 March 2018 |

**Results information**

| | |
|---|---|
| Result version number | v1 (current) |
| This version publication date | 22 September 2019 |
| First version publication date | 22 September 2019 |

## Trial information

**Trial identification**

| | |
|---|---|
| Sponsor protocol code | 08042012 |

**Additional study identifiers**

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

Notes:

**Sponsors**

| | |
|---|---|
| Sponsor organisation name | Medical University of Vienna |
| Sponsor organisation address | Spitalgasse 23, Vienna, Austria, 1090 |
| Public contact | Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, 0043 14040041000, thomas.hamp@meduniwien.ac.at |
| Scientific contact | Department of Anaesthesia, Intensive Care Medicine and Pain Medicine, Medical University of Vienna, 0043 14040041000, thomas.hamp@meduniwien.ac.at |

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 | 31 March 2018 |
| Is this the analysis of the primary completion data? | Yes |
| Primary completion date | 31 March 2018 |
| Global end of trial reached? | Yes |
| Global end of trial date | 31 March 2018 |
| Was the trial ended prematurely? | No |

Notes:

## General information about the trial

Main objective of the trial:

Does intravenous s-ketamine reduce the MAC value of Sevoflurane

Protection of trial subjects:

Adequate anaesthesia was confirmed using clinical findings and BIS monitoring.

Background therapy: -

Evidence for comparator: -

| | |
|---|---|
| Actual start date of recruitment | 01 October 2014 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | Yes |

Notes:

## Population of trial subjects

### Subjects enrolled per country

| | |
|---|---|
| Country: Number of subjects enrolled | Austria: 61 |
| Worldwide total number of subjects | 61 |
| EEA total number of subjects | 61 |

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) | 61 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

## Subject disposition

### Recruitment

Recruitment details: -

### Pre-assignment

Screening details:

Adult patients with an American Society of Anaesthesia (ASA) physical status of I to III who were scheduled for elective surgery requiring a skin incision of at least 3 cm at the trunk were eligible for enrolment in the study. Patients were screened in the pre-anesthesia clinic.

### 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, Assessor |

### Arms

| | |
|---|---|
| Are arms mutually exclusive? | Yes |
| **Arm title** | High Dose S-Ketamine Group |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | S-Ketamine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

s-ketamine was administered as a bolus of 1 mg kg−1 S-ketamine in saline, followed by continuous infusion of 1 mg kg−1 h−1 S-ketamine in saline

| | |
|---|---|
| **Arm title** | Low Dose S-Ketamine Group |

Arm description: -

| | |
|---|---|
| Arm type | Experimental |
| Investigational medicinal product name | S-Ketamine |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

s-ketamine was administered as a bolus of 0.5 mg kg−1 S-ketamine in saline, followed by continuous infusion of 0.5 mg kg−1 h−1 S-ketamine in saline

| | |
|---|---|
| **Arm title** | Placebo |

Arm description: -

| | |
|---|---|
| Arm type | Placebo |
| Investigational medicinal product name | Sodium Chloride 0.9% |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Infusion |
| Routes of administration | Intravenous use |

Dosage and administration details:

The placebo group received a bolus of 0.9% saline, followed by continuous infusion of 0.9% saline.

| **Number of subjects in period 1** | High Dose S-Ketamine Group | Low Dose S-Ketamine Group | Placebo |
|---|---|---|---|
| Started | 20 | 20 | 21 |
| Completed | 20 | 20 | 20 |
| Not completed | 0 | 0 | 1 |
| Protocol deviation | - | - | 1 |

## Baseline characteristics

| Reporting groups | |
|---|---|
| Reporting group title | overall trial |

Reporting group description: -

| Reporting group values | overall trial | Total | |
|---|---|---|---|
| Number of subjects | 61 | 61 | |
| Age categorical<br>Units: Subjects | | | |
| In utero | 0 | 0 | |
| Preterm newborn infants (gestational age < 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days-23 months) | 0 | 0 | |
| Children (2-11 years) | 0 | 0 | |
| Adolescents (12-17 years) | 0 | 0 | |
| Adults (18-64 years) | 61 | 61 | |
| From 65-84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Gender categorical<br>Units: Subjects | | | |
| Female | 61 | 61 | |
| Male | 0 | 0 | |

## End points

### End points reporting groups

| | |
|---|---|
| Reporting group title | High Dose S-Ketamine Group |
| Reporting group description: - | |
| Reporting group title | Low Dose S-Ketamine Group |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

### Primary: Minimum alveolar concentration of Sevoflurane (MAC)

| | |
|---|---|
| End point title | Minimum alveolar concentration of Sevoflurane (MAC) |

End point description:

The MAC was determined by evaluating the motor response to the initial skin incision. Investigators blinded to both the study group and the ET sevoflurane concentration were positioned at the patient's head and arms and at the patient's legs to assess motor response to the skin incision. Reaction to skin incision was classified as movement or no movement. Response to the skin incision was deemed "movement" if a gross, purposeful movement of the head or at least 1 extremity was observed within 1 minute after the skin incision.4 Coughing, bucking, and straining were not considered movement.

| | |
|---|---|
| End point type | Primary |

End point timeframe:

at time of skin incision

| End point values | High Dose S-Ketamine Group | Low Dose S-Ketamine Group | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 20 | |
| Units: percent volume/volume | | | | |
| number (confidence interval 95%) | 0.5 (0.4 to 0.8) | 0.9 (0.8 to 1.1) | 2.2 (2 to 2.4) | |

### Statistical analyses

| Statistical analysis title | Primary outcome |
|---|---|

Statistical analysis description:

Choi´s method was used for the calculation of the MAC estimators of sevoflurane, as this method has been shown to perform well relative to other estimators for up-and-down designs. We also calculated the corresponding bootstrap estimates and confidence intervals. Bootstrap estimates were calculated using 5000 bootstrap samples.

| | |
|---|---|
| Comparison groups | High Dose S-Ketamine Group v Low Dose S-Ketamine Group v Placebo |

| | |
|---|---|
| Number of subjects included in analysis | 60 |
| Analysis specification | Pre-specified |
| Analysis type | superiority |
| P-value | ≤ 0.05 [1] |
| Method | Choi´s Method |
| Parameter estimate | MAC of Sevoflurane using Choi´s Method |
| Confidence interval | |
| level | 95 % |
| sides | 2-sided |
| Variability estimate | Standard error of the mean |

Notes:

[1] - As there is no statistical test using Choi´s method for calculation of the primary outcome providing a P-value available for comparison of the MAC estimates, 95% confidence intervals were used for the interpretation of statistical significance.

## Secondary: Plasma concentration of lidocaine

| | |
|---|---|
| End point title | Plasma concentration of lidocaine |

End point description:

An arterial blood sample was taken at the time the skin incision was performed to determine the blood concentrations of S-ketamine.

| | |
|---|---|
| End point type | Secondary |

End point timeframe:

at the time of skin incision

| End point values | High Dose S-Ketamine Group | Low Dose S-Ketamine Group | Placebo | |
|---|---|---|---|---|
| Subject group type | Reporting group | Reporting group | Reporting group | |
| Number of subjects analysed | 20 | 20 | 21 | |
| Units: microgram(s)/millilitre | | | | |
| arithmetic mean (standard deviation) | 1.1 (± 1) | 0.5 (± 0.2) | 0 (± 0) | |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

| Adverse events information | |
|---|---|
| Timeframe for reporting adverse events: | |
| Entire Study period | |
| Assessment type | Non-systematic |

| Dictionary used | |
|---|---|
| Dictionary name | MedDRA |
| Dictionary version | 20 |

| Reporting groups | |
|---|---|
| Reporting group title | High Dose S-Ketamine Group |
| Reporting group description: - | |
| Reporting group title | Low Dose S-Ketamine Group |
| Reporting group description: - | |
| Reporting group title | Placebo |
| Reporting group description: - | |

| Serious adverse events | High Dose S-Ketamine Group | Low Dose S-Ketamine Group | Placebo |
|---|---|---|---|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 0 / 20 (0.00%) | 0 / 20 (0.00%) | 0 / 21 (0.00%) |
| number of deaths (all causes) | 0 | 0 | 0 |
| number of deaths resulting from adverse events | 0 | 0 | 0 |

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

| Non-serious adverse events | High Dose S-Ketamine Group | Low Dose S-Ketamine Group | Placebo |
|---|---|---|---|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 20 (0.00%) | 0 / 21 (0.00%) |
| Gastrointestinal disorders | | | |
| Nausea | | | |
| subjects affected / exposed | 2 / 20 (10.00%) | 0 / 20 (0.00%) | 0 / 21 (0.00%) |
| occurrences (all) | 2 | 0 | 0 |

## 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