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 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 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