Clinical trial results:
Determination of the minimal alveolar concentration of Sevoflurane in patient with end stage liver disease

Summary

EudraCT number	2014-001552-29
Trial protocol	AT
Global end of trial date	22 April 2017

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022

Trial information

Trial identification

Sponsor protocol code	1271/2014

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	Währinger Gürtel 18-20, Vienn, Austria, 1090
Public contact	Sekretariat, Medizinische Universität Wien, Abteilung für Anästhesie und allgemeine Intensivmedizin, 0043 1404004102,
Scientific contact	Sekretariat, Medizinische Universität Wien, Abteilung für Anästhesie und allgemeine Intensivmedizin, 0043 1404004102,

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	22 April 2017
Is this the analysis of the primary completion data?	Yes
Primary completion date	22 April 2017
Global end of trial reached?	Yes
Global end of trial date	22 April 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to determine whether patients with end stage liver disease undergoing liver transplantation have lower MAC values of sevoflurane than healthy patients.

Protection of trial subjects:

Before skin incision, acceleromyography was used to exclude residual pharmacological paralysis. The MAC of sevo!urane was determined by observing the patients' motor response to initial surgical skin incision. The motor response to skin incision was classi"ed as "response" or "no response." Investigators blinded to the actual ET sevoflurane concentration observed movements of patients' head, arms, or legs. The response was identi"ed as "response" when a gross, purposeful movement of the head or at least one extremity occurred within 1 minute after skin incision. Coughing, bucking, and straining were not noted as movement.

Background therapy: -

Evidence for comparator:

The potency of volatile anesthetics is expressed by the minimum alveolar concentration (MAC). A MAC of 1 is de"ned as the end-tidal (ET) alveolar concentration of the volatile anesthetic at 1 atmosphere, at which 50% of individuals do not move after initial skin incision.2 Maintaining ET alveolar concentrations of volatile anesthetics above 0.7 MAC during surgery is thought to decrease the incidence of awareness.3 In contrast, anesthesia with volatile anesthetics using a MAC greater than 1.25 might lead to side effects including bradycardia, hypotension, or accumulation of toxic degradation products.4,5 The MAC of sevo!urane has been extensively characterized in healthy adults, with values ranging from 1.7% ± 0.2%6 to 2.1% ± 0.1%7 but has not been assessed in patients with ESLD undergoing OLT. We hypothesized that the MAC of sevo!urane would be lower in patients with ESLD undergoing OLT than in patients with normal liver function undergoing major abdominal surgery.

Actual start date of recruitment	03 August 2014
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	Austria: 40
Worldwide total number of subjects	40
EEA total number of subjects	40

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)	40
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients between 30 and 65 years of age were enrolled in the study. The study group included patients with ESLD scheduled for OLT, whereas the control group included patients without evident liver disease undergoing major abdominal surgery requiring a laparotomy with a skin incision of at least 10 cm.

Pre-assignment

Screening details:

In patients undergoing OLT, blood ammonia concentrations and the model for endstage liver disease (MELD) score were assessed on the day of transplantation. Blood gases, the acid-base status, and electrolyte concentrations were analyzed after induction of anesthesia in all patients.

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Investigator[1]

Blinding implementation details:

In this prospective, blinded study, we compared the MAC of sevoflurane among patients with ESLD undergoing OLT and patients with normal liver function undergoing major abdominal surgery.

Arms

Are arms mutually exclusive?	Yes
Arm title	ESLD scheduled for OLT

Arm description:

In this prospective, blinded study, we compared the MAC of sevoflurane among patients with ESLD undergoing OLT

Arm type	Experimental
Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection/infusion
Routes of administration	Injection

Dosage and administration details:

Stable ET concentrations of sevofurane were reached 17 minutes (95% CI, 15–19) after initiating administration of sevoflurane in all patients (Figure&1). Steady ET concentrations of sevo!urane were maintained for 41 minutes (95% CI, 37–45) in the OLT group and for 27 minutes (95% CI, 22–32) in the control group before skin incision.

Arm title	normal liver function

Arm description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B).

The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Arm type	Experimental
Investigational medicinal product name	Sevoflurane
Investigational medicinal product code	
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Dosage and administration details:

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Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: This study was performed as a monocentric, single-blinded, prospective clinical trial at the Medical University of Vienna in accordance with the ethical standards stated in the Declaration of Helsinki.

Number of subjects in period 1	ESLD scheduled for OLT	normal liver function
Started	20	20
Completed	20	20

Baseline characteristics

Reporting groups

Reporting group title	Overall trial (overall period)

Reporting group description: -

Reporting group values	Overall trial (overall period)	Total	
Number of subjects	40	40	
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)	40	40	
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	12	12	
Male	28	28	

Subject analysis sets

Subject analysis set title	undergoing OLT 3 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	Control normal liver function 3 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	undergoing OLT 1 minutes before

Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	Control normal liver function 1 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	undergoing OLT 1 minute after skin incision
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	Control normal liver function 1minute after skin incision
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14

Reporting group values	undergoing OLT 3 minutes before	Control normal liver function 3 minutes before	undergoing OLT 1 minutes before
Number of subjects	7	8	7
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)	7	8	7
From 65-84 years	0	0	
85 years and over	0	0	
Gender categorical Units: Subjects			
Female	3	4	3
Male	4	4	4

Reporting group values	Control normal liver function 1 minutes before	undergoing OLT 1 minute after skin incision	Control normal liver function 1minute after skin incision
Number of subjects	8	7	8
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over	8	7	8
Gender categorical Units: Subjects			
Female	4	3	4
Male	4	4	4

End points

End points reporting groups

Reporting group title	ESLD scheduled for OLT

Reporting group description:

In this prospective, blinded study, we compared the MAC of sevoflurane among patients with ESLD undergoing OLT

Reporting group title	normal liver function

Reporting group description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	undergoing OLT 3 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	Control normal liver function 3 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	undergoing OLT 1 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	Control normal liver function 1 minutes before
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD

undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	undergoing OLT 1 minute after skin incision
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14–39) compared to patients with preserved liver function.

Subject analysis set title	Control normal liver function 1minute after skin incision
Subject analysis set type	Per protocol

Subject analysis set description:

By including 20 patients in each group, we obtained 7 crossovers in the OLT group and 8 crossovers in the control group. The MAC of sevoflurane in patients with ESLD undergoing OLT was 1.3% (95% CI, 1.1–1.4; Figure&2A). In comparison, the MAC of sevoflurane in patients with normal liver function was 1.7% (95% CI, 1.6–1.9; Figure& 2B). The relative reduction of the MAC in patients undergoing OLT was 26% (95% CI, 14

Primary: Patients with ESLD and with normal liver function

End point title	Patients with ESLD and with normal liver function

End point description:

End point type	Primary

End point timeframe:

3 minute before; 1 minute before; 1 minute after skin incision

End point values	undergoing OLT 3 minutes before	Control normal liver function 3 minutes before	undergoing OLT 1 minutes before	Control normal liver function 1 minutes before
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	Subject analysis set
Number of subjects analysed	7	8	7	8
Units: procent				
number (confidence interval 95%)	47 (40 to 53)	35 (31 to 40)	48 (42 to 54)	37 (33 to 43)

End point values	undergoing OLT 1 minute after skin incision	Control normal liver function 1minute after skin incision		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	7	8		

Units: procent				
number (confidence interval 95%)	57 (50 to 64)	41 (36 to 47)		

Statistical analyses

Statistical analysis title	Primary
Comparison groups	undergoing OLT 3 minutes before v Control normal liver function 3 minutes before v undergoing OLT 1 minutes before v Control normal liver function 1 minutes before v undergoing OLT 1 minute after skin incision v Control normal liver function 1minute after skin incision
Number of subjects included in analysis	45
Analysis specification	Post-hoc
Analysis type	other[1]
P-value	< 0.001
Method	Dixon up-and-down” method.

Notes:

[1] - Dixon up-and-down” method.

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Patients undergo standard electrocardiography, pulse oximetry, arterial blood pressure, capnography, nasopharyngeal temperature, and Bispectral Index . The body temperature between 35.5 and 37°C)

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	20.0

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

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: There are no non serious adverse events

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

Online references

http://www.ncbi.nlm.nih.gov/pubmed/28678075