Clinical trial results:
Effect of Supplemental Oxygen on Perioperative Brain Natriuretic Peptide Concentration in Cardiac Risk Patients - A prospective randomized clinical trial

Summary

EudraCT number	2017-003714-68
Trial protocol	AT
Global end of trial date	31 January 2020

Results information

Result version number	v1 (current)
This version publication date	01 March 2022
First version publication date	01 March 2022
Summary attachment (see zip file)	Publication (1-s2.0-S095281802100218X-main.pdf)

Trial information

Trial identification

Sponsor protocol code	1744/2017

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03366857
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Medical University of Vienna
Sponsor organisation address	Spitalgasse 23, Vienna, Austria, 1090
Public contact	Head Office, Department for Anaesthesia, Office Care and Pain Management, 0043 (0) 140400 41020, sekretariat-anaesthesie@meduniwien.ac.at
Scientific contact	Head Office, Department for Anaesthesia, Office Care and Pain Management, 0043 (0) 140400 41020, sekretariat-anaesthesie@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	12 May 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 December 2019
Global end of trial reached?	Yes
Global end of trial date	31 January 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Due to the significant reduction of BNP by inhibiting sympathic nerve activity we hypothesize that supplemental oxygen have beneficial effects in perioperative BNP release in cardiac risk patients undergoing major abdominal surgery.

Protection of trial subjects:

Patients received randomly assigned 80% versus 30% inspired oxygen concentration throughout surgery and for the first two postoperative hours. We continuously measured peripheral oxygen saturation and measured blood gas analysis hourly. In the case 30% oxygen concentration was not enough, which was defined as peripheral oxygen saturation lower than 93%, we stepwise increased oxygen contraction, to provide sufficient oxygen saturation.

Background therapy:

Perioperative treatment was performed according to clinical standard of care.

Evidence for comparator: -

Actual start date of recruitment	01 December 2017
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: 260
Worldwide total number of subjects	260
EEA total number of subjects	260

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)	41
From 65 to 84 years	203

85 years and over	16

Subject disposition

Recruitment

Recruitment details:

dWe screened the operation schedule a day before surgery for eligibility. Patients had to be at least 45 years of age and underwent non-cardiac surgery. After meeting all inclusion criteria the patients was enrolled into the study.

Pre-assignment

Screening details: -

Pre-assignment period milestones

Number of subjects started	258[1]
Number of subjects completed	258

Notes:

[1] - The number of subjects reported to have started the pre-assignment period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Surgery was postponed indefinitely.

Period 1

Period 1 title	Baseline Period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind[2]
Roles blinded	Subject, Assessor

Blinding implementation details:

Patients were not aware of the assigned oxygen concentration. Postoperative outcome assessor were no aware of the intraoperative administered oxygen concentration.

Arms

Are arms mutually exclusive?	Yes
Arm title	80% Oxygen Group

Arm description:

Patients randomly assigned to the 80% oxygen group received 80% inspired oxygen concentration throughout surgery and for the first two postoperative hours.

Arm type	Active comparator
Investigational medicinal product name	80% Oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, liquefied
Routes of administration	Inhalation use

Dosage and administration details:

80%Vol per hour study period % (V/V) percent volume/volume

Investigational medicinal product name	30% Oxygen
Investigational medicinal product code	30% Oxygen
Other name	
Pharmaceutical forms	Medicinal gas, liquefied
Routes of administration	Inhalation use

Dosage and administration details:

30%Vol per hour study period % (V/V) percent volume/volume

Arm title	30% Oxygen

Arm description:

Patients randomly assigned to the 30% oxygen group received 30% inspired oxygen concentration

throughout surgery and for the first two postoperative hours.

Arm type	Active comparator
Investigational medicinal product name	30% Oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, liquefied
Routes of administration	Inhalation use

Dosage and administration details:

30%Vol per hour study period % (V/V) percent volume/volume

Notes:

[2] - The roles blinded appear to be inconsistent with a double blind trial.

Justification: Patients and outcome assessor were blinded. Blinding of the attending physician was not possible.

Number of subjects in period 1[3]	80% Oxygen Group	30% Oxygen
Started	128	130
Completed	128	130

Notes:

[3] - The number of subjects reported to be in the baseline period are not the same as the worldwide number enrolled in the trial. It is expected that these numbers will be the same.
Justification: Surgery was postponed after randomisation indefinitely. 2 patients in the 80% oxygen were enrolled but surgery was not performed.

Baseline characteristics

Reporting groups	
Reporting group title	80% Oxygen Group
Reporting group description:	
Patients randomly assigned to the 80% oxygen group received 80% inspired oxygen concentration throughout surgery and for the first two postoperative hours.	
Reporting group title	30% Oxygen
Reporting group description:	
Patients randomly assigned to the 30% oxygen group received 30% inspired oxygen concentration throughout surgery and for the first two postoperative hours.	

Reporting group values	80% Oxygen Group	30% Oxygen	Total
Number of subjects	128	130	258
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	15	17	32
From 65-84 years	106	104	210
85 years and over	7	9	16
Age continuous			
Units: years			
median	74	74	
inter-quartile range (Q1-Q3)	70 to 78	70 to 78	-
Gender categorical			
Units: Subjects			
Female	47	38	85
Male	81	92	173

End points

End points reporting groups	
Reporting group title	80% Oxygen Group
Reporting group description:	
Patients randomly assigned to the 80% oxygen group received 80% inspired oxygen concentration throughout surgery and for the first two postoperative hours.	
Reporting group title	30% Oxygen
Reporting group description:	
Patients randomly assigned to the 30% oxygen group received 30% inspired oxygen concentration throughout surgery and for the first two postoperative hours.	

Primary: NT-proBNP Concentration	
End point title	NT-proBNP Concentration
End point description:	
End point type	Primary
End point timeframe:	
Postoperative NT-proBNP concentration was measured within 2hours after surgery and on the first and third postoperative day.	

End point values	80% Oxygen Group	30% Oxygen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	130		
Units: pg/dL				
median (inter-quartile range (Q1-Q3))	810 (409 to 2387)	989 (499 to 2005)		

Attachments (see zip file)	Oxygen SAE.xlsx

Statistical analyses

Statistical analysis title	Primary Outcome
Comparison groups	80% Oxygen Group v 30% Oxygen
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)
Parameter estimate	Median difference (final values)
Point estimate	159

Confidence interval	
level	95 %
sides	2-sided
lower limit	-123
upper limit	431

Statistical analysis title	Secondary Outcome (MINS)
Comparison groups	80% Oxygen Group v 30% Oxygen
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	non-inferiority[1]
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	0.887
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.475
upper limit	1.646

Notes:

[1] - For our secondary outcome we first performed a univariable logistic regression model (using firths correction) to analyze the influence of supplemental oxygen on the incidence of MINS. MINS was defined using the following perioperative high-sensitive Troponin T thresholds: a) troponin T of 20 to<65ng/L with an absolute change of at least 5 ng/Lor b) Troponin T level > 65ng/L. Furthermore, in patients whose Troponin T concentration was adjudicated from nonischemic
etiology were not considered.

Secondary: Myocardial Injury after non cardiac surgery (MINS)	
End point title	Myocardial Injury after non cardiac surgery (MINS)

End point description:

End point type	Secondary

End point timeframe:

Incidence of MINS within the first three days after surgery.

End point values	80% Oxygen Group	30% Oxygen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	130		
Units: number of patients	26	23		

Statistical analyses

Statistical analysis title	Myocardial Injury after non cardiac Surgery
Comparison groups	30% Oxygen v 80% Oxygen Group
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Regression, Linear
Parameter estimate	Odds ratio (OR)
Point estimate	0.887
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.475
upper limit	1.646

Other pre-specified: Exploratory Outcomes	
End point title	Exploratory Outcomes
End point description:	
Exploratory outcomes during hospitalisation include: Cardiac failure, Myocardial infarction, new-onset of cardiac arrhythmias, unplanned ICU admission, reoperation, respiratory failure, and bleeding. Exploratory outcomes within 30-day after surgery include: cardiac failure, myocardial infarction, new-onset of cardiac arrhythmias, and death at day 30	
End point type	Other pre-specified
End point timeframe:	
Exploratory outcomes include complications during hospitalisation and within 30 days after surgery.	

End point values	80% Oxygen Group	30% Oxygen		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	128	130		
Units: Number of patients	42	48		

Statistical analyses

Statistical analysis title	Exploratory Outcomes
Comparison groups	80% Oxygen Group v 30% Oxygen
Number of subjects included in analysis	258
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	< 0.05
Method	Fisher exact

Adverse events

Adverse events information[1]

Timeframe for reporting adverse events:

Adverse events has been evaluated during hospitalisation and within 30 days after surgery via phone follow-up.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	23.1

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: File with SAE was attached.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
29 August 2018	We changed our secondary outcome from postoperative plasma catecholamine concentrations (including noradrenaline, adrenaline and dopamine) to postoperative copeptin concentration measurement.

Notes:

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/34087659

http://www.ncbi.nlm.nih.gov/pubmed/34856530