Clinical trial results:
Restrictive vs. Liberal Oxygen Therapy for Trauma patients. PILOT: The TRAUMOX Trial

Summary

EudraCT number	2017-004480-12
Trial protocol	DK
Global end of trial date	24 June 2018

Results information

Result version number	v1 (current)
This version publication date	01 November 2019
First version publication date	01 November 2019

Trial information

Trial identification

Sponsor protocol code	2017-991

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03491644
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Juliane Maries Vej, Copenhagen, Denmark,
Public contact	Rigshospitalet, Rigshospitalet, 0045 35451257, josefine.stokholm.baekgaard.01@regionh.dk
Scientific contact	Rigshospitalet, Rigshospitalet, 0045 35451257, josefine.stokholm.baekgaard.01@regionh.dk

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	01 October 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	24 June 2018
Global end of trial reached?	Yes
Global end of trial date	24 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial is to evaluate whether the maintenance of pragmatic normoxia, avoiding both hyperoxic and hypoxic phases, is feasible within the first 24 hours after trauma, as it may result in a reduction of 30-day mortality and major respiratory complications within 30 days (respiratory failure, pulmonary edema, and pneumonia).
We will conduct a pilot study, where 40 patients are randomized to 24 hours of:
A. Restrictive, but sufficient oxygen treatment: lowest oxygen delivery that obtains a saturation of ≥ 94%
B. Liberal oxygen treatment: 15 L/min oxygen flow initially/ FiO_2 ≥0.8

A. within the low limits of standard of care and does not put patients at risk of receiving worse treatment.
B. as close as possible to the standard of care. As no precise guidelines on oxygen delivery for trauma patients within the first 24 hours exist, this will however inevitably vary in practice.

Protection of trial subjects:

Hourly check-ups during intervention and detailed information including available contact persons 24/7.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	03 April 2018
Long term follow-up planned	Yes
Long term follow-up rationale	Scientific research
Long term follow-up duration	1 Months
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 41
Worldwide total number of subjects	41
EEA total number of subjects	41

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)	32
From 65 to 84 years	7
85 years and over	2

Subject disposition

Recruitment

Recruitment details:

As soon as the trauma team was activated a study staff member assessed the patient for inclusion. All patients where considered temporarily without the ability to consent and therefore proxy consent was sought by a trial guardian. Randomisation was then performed, and the trauma team leader was informed of the allocation and initiated treatment.

Pre-assignment

Screening details:

Between April 4th, 2018, and May 23rd, 2018, 146 patients were screened, and we randomly assigned 41 trauma patients to receive 24 hours of restrictive (n=21) or liberal (n=20) oxygen therapy.

Period 1

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

Blinding implementation details:

Outcome assessors were blinded.

Arms

Are arms mutually exclusive?	Yes
Arm title	Restrictive oxygen

Arm description:

The restrictive group (intervention) implied the lowest dosage of oxygen (>21%) that ensured an arterial oxyhemoglobin saturation (SpO2) target of 94% either using mechanical ventilation, a non-rebreather mask, a nasal cannula, or no supplementary oxygen. Supplemental oxygen was not given unless the SpO2 was below 94% and thus, only spontaneously breathing patients without supplementary oxygen could saturate above 94%. In case the SpO2 became unmeasurable, the intervention was interrupted, and standard (liberal) treatment was applied.

Arm type	Experimental
Investigational medicinal product name	Oxygen
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Medicinal gas, compressed
Routes of administration	Nasal use, Oral use

Dosage and administration details:

The restrictive group (intervention) implied the lowest dosage of oxygen (>21%) that ensured an arterial oxyhemoglobin saturation (SpO2) target of 94% either using mechanical ventilation, a non-rebreather mask, a nasal cannula, or no supplementary oxygen. Supplemental oxygen was not given unless the SpO2 was below 94% and thus, only spontaneously breathing patients without supplementary oxygen could saturate above 94%. In case the SpO2 became unmeasurable, the intervention was interrupted, and standard (liberal) treatment was applied. The liberal group (control) was designed to mimic current practice and guidelines. 1,2 Here, non-intubated patients received 15 l/min via a non-rebreather mask and intubated patients received a FiO2 of 1.0 in the trauma bay and during intra-hospital transportation. In the operating room, ICU, post-anaesthesia care unit and ward the FiO2 could be reduced to 0.8 if an arterial oxygen saturation ≥ 98% was obtained.

Arm title	Liberal oxygen treatment

Arm description:

The liberal group (control) was designed to mimic current practice and guidelines. Here, non-intubated patients received 15 l/min via a non-rebreather mask and intubated patients received a FiO2 of 1.0 in the trauma bay and during intra-hospital transportation. In the operating room, ICU, post-anaesthesia care unit and ward the FiO2 could be reduced to 0.8 if an arterial oxygen saturation ≥ 98% was obtained.

Arm type	Designed to mimic current practice and guidelines.

No investigational medicinal product assigned in this arm

Notes:

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

Justification: Single center, open-label randomized clinical trial with regards to treatment: treating staff was aware of the patient's randomization group
Primary outcome assessors were blinded to the patients' randomization.

Number of subjects in period 1	Restrictive oxygen	Liberal oxygen treatment
Started	21	20
Completed	20	18
Not completed	1	2
Consent withdrawn by subject	1	2

Baseline characteristics

Reporting groups

Reporting group title	Intervention (overall period)

Reporting group description: -

Reporting group values	Intervention (overall period)	Total	
Number of subjects	41	41	
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)	32	32	
From 65-84 years	7	7	
85 years and over	2	2	
Age continuous Units: years			
median	52		
inter-quartile range (Q1-Q3)	44 to 62	-	
Gender categorical Units: Subjects			
Female	9	9	
Male	32	32	

End points

End points reporting groups

Reporting group title	Restrictive oxygen

Reporting group description:

The restrictive group (intervention) implied the lowest dosage of oxygen (>21%) that ensured an arterial oxyhemoglobin saturation (SpO2) target of 94% either using mechanical ventilation, a non-rebreather mask, a nasal cannula, or no supplementary oxygen. Supplemental oxygen was not given unless the SpO2 was below 94% and thus, only spontaneously breathing patients without supplementary oxygen could saturate above 94%. In case the SpO2 became unmeasurable, the intervention was interrupted, and standard (liberal) treatment was applied.

Reporting group title	Liberal oxygen treatment

Reporting group description:

The liberal group (control) was designed to mimic current practice and guidelines. Here, non-intubated patients received 15 l/min via a non-rebreather mask and intubated patients received a FiO2 of 1.0 in the trauma bay and during intra-hospital transportation. In the operating room, ICU, post-anaesthesia care unit and ward the FiO2 could be reduced to 0.8 if an arterial oxygen saturation ≥ 98% was obtained.

Primary: Incidence of 30-day mortality and major pulmonary complications (combined endpoint)

End point title	Incidence of 30-day mortality and major pulmonary complications (combined endpoint)[1]

End point description:

End point type	Primary

End point timeframe:

30-days

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: Please see the attached table and the linked published article explaining the statistics.

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41	4	6		

Attachments (see zip file)	Endpoints/endpoints eudract.docx

Statistical analyses

No statistical analyses for this end point

Secondary: Major pulmonary complicatoin

End point title	Major pulmonary complicatoin

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41	2	4		

Statistical analyses

No statistical analyses for this end point

Secondary: Mortality

End point title	Mortality

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41	2	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Desaturation (<90%) episodes

End point title	Desaturation (<90%) episodes

End point description:

There were seven episodes in four patients of desaturation (SpO2 below 90%) in the restrictive group (median 87% [87-89]) and one episode of SpO2 below 90% in the liberal group (saturation= 89%). Of note, five of the seven cases of SpO2 below 89% occurred in two patients; one patient who had just been extubated and another patient who went into cardiac arrest.

End point type	Secondary

End point timeframe:

24 hours

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41	7	1		

Statistical analyses

No statistical analyses for this end point

Secondary: Days on mechanical ventilation, median

End point title	Days on mechanical ventilation, median

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 30				
median (inter-quartile range (Q1-Q3))	0 (0 to 0.4)	0 (0 to 3)		

Statistical analyses

No statistical analyses for this end point

Secondary: Sepsis

End point title	Sepsis

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41				
number (not applicable)	1	2		

Statistical analyses

No statistical analyses for this end point

Secondary: Surgical Site Infection

End point title	Surgical Site Infection

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41	1	0		

Statistical analyses

No statistical analyses for this end point

Secondary: Glasgow Outcome Scale Score

End point title	Glasgow Outcome Scale Score

End point description:

End point type	Secondary

End point timeframe:

Values of 1-8 can be obtained

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	16	17		
Units: 41				
median (inter-quartile range (Q1-Q3))	5.5 (4 to 6)	5 (3 to 5.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Intensive Care Unit admission

End point title	Intensive Care Unit admission

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41	11	10		

Statistical analyses

No statistical analyses for this end point

Secondary: ICU length of stay

End point title	ICU length of stay

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41				
median (inter-quartile range (Q1-Q3))	4.2 (1.2 to 14.5)	5.9 (0.7 to 11.7)		

Statistical analyses

No statistical analyses for this end point

Secondary: Hospital length of stay

End point title	Hospital length of stay

End point description:

End point type	Secondary

End point timeframe:

30 days

End point values	Restrictive oxygen	Liberal oxygen treatment		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	20	18		
Units: 41				
median (inter-quartile range (Q1-Q3))	1.8 (0.9 to 10.5)	5.5 (1.1 to 8.6)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

In-hospital

Adverse event reporting additional description:

As this group of patients is expected to have a lot of complications, we will report ONLY serious adverse events (SAE) and adverse events related to study outcome: pulmonary complications, sepsis and surgical site infecton.

Assessment type	Systematic

Dictionary used

Dictionary name	None
Dictionary version	0

Reporting groups

Reporting group title	Restrictive oxygen

Reporting group description:

As this group of patients is expected to have a lot of complications, we will report ONLY serious adverse events (SAE). Investigator will report them to the sponsor within 24 hours.
SAEs consist of events that result in death, are life threatening, involve hospitalization, are permanently debilitating or involve a congenital anomaly.
Furthermore, we will report adverse events related to our study outcomes:
- All pulmonary complications (Pneumonia, ALI, ARDS, atelectasis)
- Sepsis
- SSI

…before the time of discharge.

Reporting group title	Liberal oxygen treatment

Reporting group description:

As this group of patients is expected to have a lot of complications, we will report ONLY serious adverse events (SAE). Investigator will report them to the sponsor within 24 hours.
SAEs consist of events that result in death, are life threatening, involve hospitalization, are permanently debilitating or involve a congenital anomaly.
Furthermore, we will report adverse events related to our study outcomes:
- All pulmonary complications (Pneumonia, ALI, ARDS, atelectasis)
- Sepsis
- SSI

…before the time of discharge.

Serious adverse events	Restrictive oxygen	Liberal oxygen treatment	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 21 (0.00%)	0 / 20 (0.00%)	
number of deaths (all causes)	2	2	
number of deaths resulting from adverse events	0	0	

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

Non-serious adverse events	Restrictive oxygen	Liberal oxygen treatment	
Total subjects affected by non-serious adverse events subjects affected / exposed	4 / 21 (19.05%)	6 / 20 (30.00%)	
Infections and infestations			
Pneumonia or ARDS			
subjects affected / exposed	2 / 21 (9.52%)	4 / 20 (20.00%)	
occurrences (all)	2	4	
Sepsis			
subjects affected / exposed	1 / 21 (4.76%)	2 / 20 (10.00%)	
occurrences (all)	1	2	
Surgical Site Infection			
subjects affected / exposed	1 / 21 (4.76%)	0 / 20 (0.00%)	
occurrences (all)	1	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