Clinical trial results:
Endothelial Dysfunction in Resuscitated Cardiac Arrest (ENDR-RCA): Safety and efficacy of low-dose Iloprost administration and blood pressure target in addition to standard therapy, as compared to standard therapy alone, in post-cardiac-arrest-syndrome patients – a randomized, controlled, double-blinded investigator-initiated trial.

Summary

EudraCT number	2014-002998-11
Trial protocol	DK
Global end of trial date	27 February 2017

Results information

Result version number	v1 (current)
This version publication date	30 April 2020
First version publication date	30 April 2020

Trial information

Trial identification

Sponsor protocol code	ENDO-RCA

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02685618
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet, Capital Region Bloodbank 2034, Section for Transfusion Medicine
Sponsor organisation address	Blegdamsvej 9, Copenhagen, Denmark, DK-2100
Public contact	Sponsor (Pär I. Johansson), Rigshospitalet, Capital Region Bloodbank 2034, Section for Transfusion Medicine, 0045 35452030, per.johansson@regionh.dk
Scientific contact	Sponsor (Pär I. Johansson), Rigshospitalet, Capital Region Bloodbank 2034, Section for Transfusion Medicine, 0045 35452030, per.johansson@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	No

1901/2006 apply to this trial?	

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	21 October 2019
Is this the analysis of the primary completion data?	Yes
Primary completion date	27 February 2017
Global end of trial reached?	Yes
Global end of trial date	27 February 2017
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assessment of the safety and efficacy of low-dose Iloprost administration on endothelial damage and blood pressure in post-cardiac-arrest-syndrome patients. To evaluate a possible interaction between exogenously administered catecholamines and iloprost efficacy on the endothelium.

Protection of trial subjects:

All patients receive standard of care treatment including standardized temperature management and guideline supported achievement of mean arterial artery pressure using noradrenalin and dopamin during the intensive unit care stay.
Patients with ROSC (return of spontaneous circulation) above 240 minuts before screening, un-witnessed arrest with systoles as the initial rhythm, suspected or known acute intracranial hemorrhage or stroke were excluded from the trial.
Patients are in a critical acute condition resulting in mental impairment or sedation, therefore scientific guardians will co-sign the informed consent form. Next-of-kin and the patients' general practitioner will co-sign.

Background therapy:

Standard of care.

Evidence for comparator:

saline is used as placebo in this trial.

Actual start date of recruitment	25 February 2016
Long term follow-up planned	Yes
Long term follow-up rationale	Safety, Efficacy, Scientific research
Long term follow-up duration	6 Months
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Denmark: 46
Worldwide total number of subjects	46
EEA total number of subjects	46

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)	26
From 65 to 84 years	19
85 years and over	1

Subject disposition

Recruitment

Recruitment details:

Recruitment period 01.03.2016 to 31.08.2016.
All patients were recruited at: Department Cardiology 2143, Copenhagen University Hospital, Denmark.
Inclusion criteria were patients 18 years or older with (out-of-hospital-cardiac-arrest (OHCA)

Pre-assignment

Screening details:

A total of 77 patients were pre-screened of these 66 patients were assessed for eligibility. Of these 50 patients were randomised but only 46 patients were included in the trial of these 40 completed the 96-hour endpoint. Patients were recruited in 1:2 ration (active:placebo).

Pre-assignment period milestones

Number of subjects started	50[1]
Number of subjects completed	46

Pre-assignment subject non-completion reasons

Reason: Number of subjects	other nationality: 1
Reason: Number of subjects	Consent withdrawn by subject: 1
Reason: Number of subjects	Died prior to intervention: 1
Reason: Number of subjects	Protocol deviation: 1

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: A total of 4 patients were not included in the trial.

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	Investigator, Monitor, Data analyst, Subject, Carer, Assessor

Blinding implementation details:

To circumvent selection bias, researchers and healthcare personnel was blinded to the treatment assignment. furthermore, to avoid investigator, healthcare staff and patient performance and detection bias, patients was randomized by computer to receive either iloprost or placebo similar in colour, consistency and volumen. Unblinded study nurse performed preparation of the study drug.

Arms

Are arms mutually exclusive?	Yes
Arm title	Iloprost

Arm description:

Patients receiving iloprost.

Arm type	Experimental
Investigational medicinal product name	Iloprost
Investigational medicinal product code	
Other name	Ilomedin
Pharmaceutical forms	Concentrate and solvent for solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Administration of 1 ng/kg/min for 48 hours.
Iloprost was diluated in 0.9% saline to a final volumen of 100 ml. Infusion rate was 4 ml / hours.

Investigational medicinal product name	Isotonic saline
Investigational medicinal product code	
Other name	natriumchloride 0.9%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Iloprost is diluted into saline to a final volumen of 100 ml

Arm title	Placebo

Arm description:

Saline infusion 0.9%

Arm type	Placebo
Investigational medicinal product name	isotonic saline
Investigational medicinal product code	
Other name	natriumchloride 0.9%
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Infusion: 0.9% saline to a final volumen of 100 ml with an infusion rate of 4 ml/hours for 48 hours.

Number of subjects in period 1	Iloprost	Placebo
Started	13	33
Completed	11	33
Not completed	2	0
Adverse event, serious fatal	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Iloprost
Reporting group description: Patients receiving iloprost.	
Reporting group title	Placebo
Reporting group description: Saline infusion 0.9%	

Reporting group values	Iloprost	Placebo	Total
Number of subjects	13	33	46
Age categorical Units: Subjects			
Adults (18-64 years)	9	15	24
From 65-84 years	4	17	21
85 years and over	0	1	1
Age continuous Units: years			
median	57	63	
inter-quartile range (Q1-Q3)	50 to 67	55 to 69	-
Gender categorical Units: Subjects			
Female	4	2	6
Male	9	31	40

End points

End points reporting groups

Reporting group title	Iloprost
Reporting group description:	
Patients receiving iloprost.	
Reporting group title	Placebo
Reporting group description:	
Saline infusion 0.9%	

Primary: Change in endothelial biomarkers

End point title	Change in endothelial biomarkers
End point description:	
Change in biomarkers of endothelial damage at 48 hours post baseline. The 2 arms were compared using baseline corrected Proc Mixed repeated measurement models.	
End point type	Primary
End point timeframe:	
At 48 hours post baseline	

End point values	Iloprost	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	33		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))				
Thrombomodulin	6.91 (5.75 to 9.76)	8.57 (7.77 to 11.20)		
E-Selectin	99.44 (82.43 to 123.73)	123.62 (95.04 to 146.51)		
VEcad	2005.60 (1709.70 to 2458.40)	1896.90 (1773.60 to 2372.50)		
VEGF	24.45 (15.10 to 33.85)	28.39 (14.22 to 50.49)		
Syndecan	27.21 (17.03 to 46.70)	42.02 (29.78 to 64.47)		

Attachments (see zip file)	Endothel biomarkører - ENDO-RCA.pdf

Statistical analyses

Statistical analysis title	Thrombomodulin
Statistical analysis description:	
Change in the biomarker thrombomodulin from baseline to 48 hours.	
Comparison groups	Iloprost v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	= 0.16 [2]
Method	Mixed models analysis

Notes:

[1] - Exploratory

[2] - Group*Time at the 48-hour endpoints

Statistical analysis title	Syndecain

Statistical analysis description:

Change in the biomarker syndecain from baseline to 48 hours.

Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.12 [4]
Method	Mixed models analysis

Notes:

[3] - Exploratory

[4] - Group*Time at the 48-hour endpoints

Statistical analysis title	VEcad

Statistical analysis description:

Change in the biomarker VE-Cadherine from baseline to 48 hours.

Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	= 0.81 [6]
Method	Mixed models analysis

Notes:

[5] - Exploratory

[6] - Group*Time at the 48-hour endpoints

Statistical analysis title	E-Selectin

Statistical analysis description:

Change in the biomarker E-selectin from baseline to 48 hours.

Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.1 [8]
Method	Mixed models analysis

Notes:

[7] - Exploratory

[8] - Group*Time at the 48-hour endpoints

Statistical analysis title	VEGF

Statistical analysis description:

Change in the biomarker VEGF from baseline to 48 hours.

Comparison groups	Iloprost v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.6 [10]
Method	Mixed models analysis

Notes:

[9] - Exploratory

[10] - Group*Time at the 48-hour endpoints

Primary: Chnage in plasma levels of Adrenaline/Noradrenaline

End point title	Chnage in plasma levels of Adrenaline/Noradrenaline

End point description:

Change in plasma levels over time from baseline to 48 hours. The 2 arms were compaired using baseline corected proc Mixed models

End point type	Primary

End point timeframe:

At 48 hours post baseline

End point values	Iloprost	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	11	33		
Units: pg/L				
median (inter-quartile range (Q1-Q3))				
Adrenaline	27.06 (15.71 to 239.31)	55.20 (33.73 to 165.93)		
Noradrenaline	1159.00 (398.59 to 2706.68)	1608.65 (491.16 to 5137.72)		

Statistical analyses

Statistical analysis title	Change in adrenaline level at 48 h

Statistical analysis description:

Change in plasma levels over time from baseline to 48 hours

Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.88 [11]
Method	Mixed models analysis

Notes:

[11] - Group*Time at the 48-hour endpoints

Statistical analysis title	Change in noradrenaline level at 48 h

Statistical analysis description:

Change in plasma levels over time from baseline to 48 hours

Comparison groups	Iloprost v Placebo

Number of subjects included in analysis	44
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.89 [12]
Method	Mixed models analysis

Notes:

[12] - Group*Time at the 48-hour endpoints

Primary: Change in endothelial biomarker (sTM) at 96 hours

End point title	Change in endothelial biomarker (sTM) at 96 hours

End point description:

Changes in endothelial damage and activation from baseline. The 2 arms were compared using baseline corrected proc Mixed models

End point type	Primary

End point timeframe:

At 96 hours post baseline

End point values	Iloprost	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	10	30		
Units: ng/ml				
median (inter-quartile range (Q1-Q3))				
Thrombomodulin	7.11 (6.78 to 9.94)	7.56 (5.53 to 8.86)		

Statistical analyses

Statistical analysis title	Endpoint sTM at 96 hours
Comparison groups	Placebo v Iloprost
Number of subjects included in analysis	40
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.021 [13]
Method	Mixed models analysis
Parameter estimate	Mean difference (final values)
Point estimate	1.0909
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7426
upper limit	1.4392
Variability estimate	Standard error of the mean
Dispersion value	0.6966

Notes:

[13] - Group*Time at the 96-hour endpoints

Other pre-specified: Mortality	
End point title	Mortality
End point description: Number of death within 30, 90 and 180 days post baseline	
End point type	Other pre-specified
End point timeframe: 30, 90 and 180 days post intervention	

End point values	Iloprost	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	13	33		
Units: number				
Death within 30 days	6	8		
Death within 90 days	6	8		
Death within 180 days	8	8		

Statistical analyses

Statistical analysis title	90-day mortality
Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14
Method	Fisher exact

Statistical analysis title	180-day mortality
Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.02
Method	Fisher exact
Parameter estimate	Log hazard ratio
Point estimate	2.84
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.1
upper limit	7.4

Statistical analysis title	30-day mortality
Comparison groups	Iloprost v Placebo
Number of subjects included in analysis	46
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14
Method	Fisher exact

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Adverse events are reported until day 30 post intervention start	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	10

Reporting groups	
Reporting group title	Intervention
Reporting group description:	
The 13 patients in this intervention group	
Reporting group title	Placebo
Reporting group description:	
All patients receiving placebo	

Serious adverse events	Intervention	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	2 / 13 (15.38%)	3 / 33 (9.09%)	
number of deaths (all causes)	8	8	
number of deaths resulting from adverse events	0	0	
Vascular disorders			
Hypotension			
subjects affected / exposed	2 / 13 (15.38%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Lower gastrointestinal haemorrhage			
subjects affected / exposed	0 / 13 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
traumatic bleeding			
subjects affected / exposed	0 / 13 (0.00%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 2 %

Non-serious adverse events	Intervention	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	8 / 13 (61.54%)	19 / 33 (57.58%)	
Vascular disorders			
Thrombocytopenia			
subjects affected / exposed	3 / 13 (23.08%)	9 / 33 (27.27%)	
occurrences (all)	3	9	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	4 / 13 (30.77%)	9 / 33 (27.27%)	
occurrences (all)	4	9	
Seizure			
subjects affected / exposed	1 / 13 (7.69%)	1 / 33 (3.03%)	
occurrences (all)	1	1	

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

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

Electronic randomization allocation patients in a 2:1 manner instead of 1:1. The randomization allocation 1:2 resulted in a small sample size in the iloprost group with increased risk of type I and type II errors. Also limitation due to pilot trial

Notes:

Online references

http://www.ncbi.nlm.nih.gov/pubmed/31710844

http://www.ncbi.nlm.nih.gov/pubmed/31945586