Clinical trial results:
STEROID TREATMENT AS ANTI-INFLAMMATORY AND NEUROPROTECTIVE AGENT FOLLOWING OUT-OF-HOSPITAL CARDIAC ARREST. A RANDOMIZED TRIAL.

Summary

EudraCT number	2020-000855-11
Trial protocol	DK
Global end of trial date	28 February 2023

Results information

Result version number	v1 (current)
This version publication date	10 February 2024
First version publication date	10 February 2024

Trial information

Trial identification

Sponsor protocol code	HJE-STEROHCA-001

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT04624776
WHO universal trial number (UTN)	-
Other trial identifiers	The STEROHCA Trial: Acronym

Notes:

Sponsors

Sponsor organisation name	Rigshospitalet
Sponsor organisation address	Blegdamsvej 9, Copenhagen OE, Denmark, 2100
Public contact	Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, 45 35450572, christian.hassager@regionh.dk
Scientific contact	Department of Cardiology, Copenhagen University Hospital, Rigshospitalet, 45 35450572, christian.hassager@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	28 February 2023
Is this the analysis of the primary completion data?	Yes
Primary completion date	15 July 2022
Global end of trial reached?	Yes
Global end of trial date	28 February 2023
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Patients suffering from out-of-hospital cardiac arrest (OHCA) who remain in a comatose state post-resuscitation face elevated risk of mortality due to the post-cardiac arrest syndrome (PCAS). PCAS features systemic inflammation, which is associated to poor outcomes in OHCA. Hence, attenuating inflammation could potentially be beneficial following OHCA. The primary objective of this trial was to determine the efficacy of the anti-inflammatory glucocorticoid "methylprednisolone" compared with placebo. The co-primary endpoints were serial measurements of interleukin-6 and neuron-specific-enolase as markers of systemic inflammation and brain injury at admission and 24, 48 and 72 hours after admission in patients admitted after resuscitated OHCA. The secondary endpoints included other biomarkers for inflammation and brain injury, markers of organ injury, safety, and survival.
The primary results have been published: https://doi.org/10.1007/s00134-023-07247-w

Protection of trial subjects:

All patients included in the trial were treated according to international post-resuscitation guidelines, and trial participation did not restrict additional treatment. Concurrent enrollment in other trials was permissible. Patients were screened for contraindications to the intervention before enrollment, and the trial was monitored and evaluated for safety throughout the study period. The intervention, methylprednisolone, has known immunosuppressive effects and can induce hyperglycemia, but as part of standard of care, all patients received prophylactic antibiotics to potentially reduce the incidence of infections and continuous intravenous insulin for hyperglycaemia during the initial intensive care unit stay.

Background therapy:

After resuscitated out-of-hospital cardiac arrest, patients underwent standard care following International post-resuscitation guidelines. This included targeted temperature management at 36°C for comatose patients, sedation primarily utilizing propofol and fentanyl, and the administration of vasopressors and inotropes as necessary. Furthermore, all comatose patients received prophylactic antibiotic treatment with intravenous piperacillin/tazobactam or cefuroxime in the event of a β-lactam allergy. Continuous intravenous insulin was also administered to address hyperglycemia.

Evidence for comparator:

No significant effect was expected by the comparator (Placebo: isotonic saline 0.9%)

Actual start date of recruitment	10 October 2020
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: 137
Worldwide total number of subjects	137
EEA total number of subjects	137

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)	58
From 65 to 84 years	74
85 years and over	5

Subject disposition

Recruitment

Recruitment details:

The recruitment period was completed in 21 months (expected period was 18 months as defined in the protocol)

Pre-assignment

Screening details:

In the study period, 207 out of 1976 patients in the study region were eligible for inclusion, with 158 patients being randomized (80 methylprednisolone, 78 placebo). Of these, 137 patients encompassed the modified intention-to-treat (21 patients excluded; methylprednisolone 12, placebo 9), which this report is based on.

Period 1

Period 1 title	Overall trial period (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Blinding implementation details:

After opening a medicine box, the including prehospital physician and accompanying medical assistant became unblinded. Subsequently, the prehospital staff played no further role in the patient's treatment or the study post-admission. Treatment allocation remained blinded for the patient, all hospital personnel, as well as all study investigators and staff.

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Saline
Investigational medicinal product code	
Other name	Isotonic saline, NaCl 0.9%
Pharmaceutical forms	Solution for injection
Routes of administration	Intraosseous use, Intravenous use

Dosage and administration details:

Placebo consisted of administration of 4 mL of isotonic saline (NaCl 0.9%)

Arm title	Methylprednisolone

Arm description: -

Arm type	Experimental
Investigational medicinal product name	Solu-medrol
Investigational medicinal product code	6132
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Intraosseous use, Intravenous use

Dosage and administration details:

A dosis of 250 mg methylprednisolone suspended in isotonic saline to a total volume of 4 mL prior to infusion. Administration was done over a period of minimum 5 minutes.

Number of subjects in period 1	Placebo	Methylprednisolone
Started	69	68
Completed	69	68

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Methylprednisolone
Reporting group description: -	

Reporting group values	Placebo	Methylprednisolone	Total
Number of subjects	69	68	137
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			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)			0
From 65-84 years			0
85 years and over			0
Age continuous			
Age at time of OHCA			
Units: years			
median	66	67	
inter-quartile range (Q1-Q3)	56 to 75	57 to 74	-
Gender categorical Units: Subjects			
Female	13	12	25
Male	56	56	112

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Methylprednisolone
Reporting group description: -	

Primary: Interleukin 6, IL-6

End point title	Interleukin 6, IL-6
End point description:	
End point type	Primary
End point timeframe:	
Measured at admission, 24, 48, and 72 hours	

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: pg/mL				
geometric mean (confidence interval 95%)				
Admission	15.0 (10.4 to 21.7)	15.0 (10.4 to 21.6)		
24 hours	29.8 (18.9 to 46.8)	2.1 (1.3 to 3.2)		
48 hours	10.1 (6.7 to 15.1)	5.7 (3.8 to 8.4)		
72 hours	3.4 (2.2 to 5.4)	4.3 (2.7 to 6.6)		

Statistical analyses

Statistical analysis title	Interleukin 6, mixed model analysis
Statistical analysis description:	
Interleukin 6 levels from admission to 72 hours after admission	
Comparison groups	Placebo v Methylprednisolone
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	≤ 0.0001 [2]
Method	Mixed models analysis

Notes:

[1] - Linear mixed model without baseline adjustment

[2] - P value for the treatment-by-time interaction listed above. Time specific comparisons of methylprednisolone vs placebo at admission: p=0.9, 24 hours: p<0.0001, 48 hours: p=0.05, and 72 hours: p=0.5.

Primary: Neuron-specific enolase, NSE

End point title	Neuron-specific enolase, NSE

End point description:

End point type	Primary

End point timeframe:

Measured at admission, 24, 48, and 72 hours

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: ug/L				
geometric mean (confidence interval 95%)				
Admission	17.2 (14.8 to 20.0)	19.6 (16.9 to 22.7)		
24 hours	17.2 (14.3 to 20.7)	19.1 (15.9 to 22.9)		
48 hours	14.8 (11.2 to 19.4)	18.8 (14.4 to 24.6)		
72 hours	14.7 (11.1 to 19.5)	15.7 (11.9 to 20.9)		

Statistical analyses

Statistical analysis title	Neuron-specific enolase, mixed model analysis

Statistical analysis description:

Neuron-specific enolase levels from admission to 72 hours after admission

Comparison groups	Methylprednisolone v Placebo
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[3]
P-value	= 0.22 [4]
Method	Mixed models analysis

Notes:

[3] - Linear mixed model without baseline adjustment

[4] - P value for the treatment-by-time interaction listed above. Time specific comparisons of methylprednisolone vs placebo at admission: p=0.24, 24 hours: p=0.42, 48 hours: p=0.21, and 72 hours: p=0.75.

Secondary: Survival after 180 days

End point title	Survival after 180 days

End point description:

End point type	Secondary

End point timeframe:

Survival 180 days after cardiac arrest

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: No.				
number (not applicable)				
Alive at 180 days	44	51		

Statistical analyses

Statistical analysis title	Survival after 180 days
Comparison groups	Placebo v Methylprednisolone
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.17
Method	Regression, Cox
Parameter estimate	Hazard ratio (HR)
Point estimate	0.65
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.35
upper limit	1.2

Secondary: Cerebral Performance Category (CPC) after 180 days

End point title	Cerebral Performance Category (CPC) after 180 days

End point description:

A score of ≥3 indicating a poor neurologic outcome, including death

End point type	Secondary

End point timeframe:

CPC evaluated 180 days after cardiac arrest

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Score				
number (not applicable)				
180 days after cardiac arrest	26	19		

Statistical analyses

Statistical analysis title	CPC score 180 days after OHCA
Statistical analysis description:	
Comparing poor neurologic outcome (score ≥3) in the two treatment arms	
Comparison groups	Placebo v Methylprednisolone
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.28
Method	Fisher exact

Secondary: Modified Rankin Scale (mRS) after 180 days

End point title	Modified Rankin Scale (mRS) after 180 days
End point description:	
A score of ≥4 indicating a poor neurologic outcome, including death	
End point type	Secondary
End point timeframe:	
mRS evaluated 180 days after cardiac arrest	

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: Score				
number (not applicable)				
180 days after cardiac arrest	17	26		

Statistical analyses

Statistical analysis title	mRS score 180 days after OHCA
Statistical analysis description:	
Comparing poor neurologic outcome (score ≥4) in the two treatment arms	
Comparison groups	Placebo v Methylprednisolone

Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.14
Method	Fisher exact

Secondary: C-reactive protein, CRP

End point title	C-reactive protein, CRP

End point description:

End point type	Secondary

End point timeframe:

Measured at admission, 24, 48, and 72 hours

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: mg/L				
geometric mean (confidence interval 95%)				
Admission	3.15 (2.18 to 4.13)	2.13 (1.49 to 2.78)		
24 hours	72.40 (55.91 to 88.89)	24.90 (19.31 to 30.49)		
48 hours	122.82 (90.08 to 155.56)	35.58 (26.28 to 44.89)		
72 hours	96.46 (69.61 to 123.30)	45.35 (32.88 to 57.81)		

Statistical analyses

Statistical analysis title	CRP, mixed model analysis

Statistical analysis description:

CRP levels from admission to 72 hours after admission

Comparison groups	Placebo v Methylprednisolone
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[5]
P-value	< 0.0001 [6]
Method	Mixed models analysis

Notes:

[5] - Linear mixed model without baseline adjustment

[6] - P value for the treatment-by-time interaction listed above. Time specific comparisons of methylprednisolone vs placebo at admission: p=0.08, 24 hours: p <0.0001, 48 hours: p<0.0001, and

72 hours: p<0.001.

Secondary: Neurofilament light chain, NfL	
End point title	Neurofilament light chain, NfL
End point description:	
End point type	Secondary
End point timeframe:	
Measured at admission, 24, 48, and 72 hours	

End point values	Placebo	Methylprednisolone		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	69	68		
Units: pg/mL				
geometric mean (confidence interval 95%)				
Admission	68.3 (54.3 to 82.2)	68.0 (53.9 to 82.2)		
24 hours	184.1 (98.0 to 270.2)	190.4 (103.2 to 277.5)		
48 hours	230.5 (110.3 to 350.7)	248.8 (121.9 to 375.8)		
72 hours	243.2 (120.0 to 366.3)	263.2 (132.8 to 393.6)		

Statistical analyses

Statistical analysis title	NfL, mixed model analysis
Statistical analysis description:	
NfL levels from admission to 72 hours after admission	
Comparison groups	Placebo v Methylprednisolone
Number of subjects included in analysis	137
Analysis specification	Pre-specified
Analysis type	other[7]
P-value	= 0.96 [8]
Method	Mixed models analysis

Notes:

[7] - Linear mixed model without baseline adjustment

[8] - P value for the treatment-by-time interaction listed above. Time specific comparisons of methylprednisolone vs placebo at admission: p=0.9, 24 hours: p=0.9, 48 hours: p=0.8, and 72 hours: p=0.8.

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From time of randomization till 180 days after cardiac arrest	
Assessment type	Systematic

Dictionary used	
Dictionary name	Study protocol
Dictionary version	3.1

Reporting groups	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Methylprednisolone
Reporting group description: -	

Serious adverse events	Placebo	Methylprednisolone	
Total subjects affected by serious adverse events			
subjects affected / exposed	37 / 69 (53.62%)	35 / 68 (51.47%)	
number of deaths (all causes)	25	17	
number of deaths resulting from adverse events			
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	10 / 69 (14.49%)	7 / 68 (10.29%)	
occurrences causally related to treatment / all	0 / 10	0 / 7	
deaths causally related to treatment / all	0 / 2	0 / 1	
Nervous system disorders			
Seizure			
subjects affected / exposed	13 / 69 (18.84%)	12 / 68 (17.65%)	
occurrences causally related to treatment / all	0 / 13	0 / 12	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Bleeding	Additional description: Defined as the occurrence of bleeding, either diagnosed in-hospital or requiring in-hospital treatment.		
subjects affected / exposed	4 / 69 (5.80%)	0 / 68 (0.00%)	
occurrences causally related to treatment / all	0 / 4	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Electrolyte imbalance			

subjects affected / exposed	1 / 69 (1.45%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Dialysis			
subjects affected / exposed	1 / 69 (1.45%)	2 / 68 (2.94%)	
occurrences causally related to treatment / all	0 / 2	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	4 / 69 (5.80%)	5 / 68 (7.35%)	
occurrences causally related to treatment / all	0 / 4	0 / 6	
deaths causally related to treatment / all	0 / 0	0 / 0	
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	0 / 69 (0.00%)	1 / 68 (1.47%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 1 %

Non-serious adverse events	Placebo	Methylprednisolone	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	33 / 69 (47.83%)	49 / 68 (72.06%)	
Cardiac disorders			
Arrhythmia			
subjects affected / exposed	7 / 69 (10.14%)	7 / 68 (10.29%)	
occurrences (all)	8	9	
Nervous system disorders			
Seizure			
subjects affected / exposed	1 / 69 (1.45%)	0 / 68 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Bleeding			
subjects affected / exposed	3 / 69 (4.35%)	2 / 68 (2.94%)	
occurrences (all)	3	2	

Electrolyte imbalance subjects affected / exposed occurrences (all)	15 / 69 (21.74%) 17	25 / 68 (36.76%) 30	
Infections and infestations Infection subjects affected / exposed occurrences (all)	4 / 69 (5.80%) 5	2 / 68 (2.94%) 3	
Metabolism and nutrition disorders Metabolic disorder subjects affected / exposed occurrences (all)	8 / 69 (11.59%) 8	27 / 68 (39.71%) 30	

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/36414975

http://www.ncbi.nlm.nih.gov/pubmed/37943300