Clinical trial results:
Infusion of hypertonic solutions: A risk factor for delirium after cardiac surgery? A randomised double blinded controlled trial.

Summary

EudraCT number	2018-002385-39
Trial protocol	SE
Global end of trial date	26 June 2020

Results information

Result version number	v1 (current)
This version publication date	03 June 2021
First version publication date	03 June 2021

Trial information

Trial identification

Sponsor protocol code	HSPOD

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	County Council of Västerbotten
Sponsor organisation address	Heart Center, University Hospital of Umeå, Umeå, Sweden,
Public contact	Fredrik Holmner, County Council of Västerbotten, 046 0907853650, fredrik.holmner@vll.se
Scientific contact	Fredrik Holmner, County Council of Västerbotten, 046 0907853650, fredrik.holmner@vll.se

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	26 June 2020
Is this the analysis of the primary completion data?	Yes
Primary completion date	26 June 2020
Global end of trial reached?	Yes
Global end of trial date	26 June 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Are hypertonic solutions a risk factor for delirium after cardiac surgery?

Protection of trial subjects:

All patients was informed about the strict confidentiality of their patient data, but that their medical records may be reviewed for trial purposes by authorized individuals other than their treating physician Personal data was processed in a legal, correct and open manner, collected for specific, explicit and legitimate purposes, adequate and relevant, correct and updated. Personal data are stored in a form that allows identification of the data patient for a longer time than is necessary and was treated in a manner that ensures appropriate security.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	26 April 2019
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	Sweden: 205
Worldwide total number of subjects	205
EEA total number of subjects	205

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)	1
From 65 to 84 years	204
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were enrolled consecutively and upon availability at Umeå Heart Centre, Umeå University Hospital, Sweden, between April 2019 and June 2020

Pre-assignment

Screening details:

205 patients were included, 200 were randomised

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	Subject, Investigator, Data analyst

Arms

Are arms mutually exclusive?	Yes
Arm title	Test group

Arm description:

Cardiac surgical patients requiring cardiopulmonary bypass randomised to:
Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU

Arm type	Experimental
Investigational medicinal product name	Ringer-Acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intraarterial use

Dosage and administration details:

1000 ml administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

Investigational medicinal product name	Mannitol
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intraarterial use

Dosage and administration details:

60 g administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

Investigational medicinal product name	Sodium chloride
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate for concentrate for solution for infusion
Routes of administration	Intraarterial use

Dosage and administration details:

160 mmol administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	

Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intraarterial use

Dosage and administration details:

10 000 IU administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

Arm title	Comparison group

Arm description:

Cardiac surgical patients requiring cardiopulmonary bypass randomised to:
Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU

Arm type	Active comparator
Investigational medicinal product name	Ringer-Acetate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intraarterial use

Dosage and administration details:

1400 ml administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

Investigational medicinal product name	Heparin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for solution for injection/infusion
Routes of administration	Intraarterial use

Dosage and administration details:

10 000 IU administered at commence of cardiopulmonary bypass as a single dose. Included in the prime composition used to fill the components of the heart-lung machine.

Number of subjects in period 1[1]	Test group	Comparison group
Started	100	100
Completed	98	97
Not completed	2	3
Consent withdrawn by subject	-	3
Lost to follow-up	1	-
Protocol deviation	1	-

Notes:

[1] - 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: 205 patients were included, only 200 were randomised due to change of ECC method after inclusion (heparin coated CPB system)

Baseline characteristics

Reporting groups	
Reporting group title	Test group
Reporting group description:	
Cardiac surgical patients requiring cardiopulmonary bypass randomised to: Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU	
Reporting group title	Comparison group
Reporting group description:	
Cardiac surgical patients requiring cardiopulmonary bypass randomised to: Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU	

Reporting group values	Test group	Comparison group	Total
Number of subjects	100	100	200
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)	1	0	1
From 65-84 years	99	100	199
85 years and over	0	0	0
Gender categorical Units: Subjects			
Female	30	24	54
Male	70	76	146

End points

End points reporting groups

Reporting group title	Test group
Reporting group description:	
Cardiac surgical patients requiring cardiopulmonary bypass randomised to: Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU	
Reporting group title	Comparison group
Reporting group description:	
Cardiac surgical patients requiring cardiopulmonary bypass randomised to: Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU	

Primary: Delirium

End point title	Delirium

End point description:

Assessment delirium is performed by executing the following test battery:
1. Mini Mental State Examination (MMSE)
2. Geriatric Depression Scale-15 (GDS-15)
3. Katz ADL-stair case test
4. Barthel index
5. NRS Pain
6. Organic Brain Syndrome Scale (OBS)
7. The Nursing Delirium Screening Scale (Nu-DESC)
8. Richmond agitation sedation scale (RASS)
9. Glasgow coma scale (GCS)

End point type	Primary

End point timeframe:

Assessed before and 1 day and 3 days after surgery

End point values	Test group	Comparison group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: number of patients	98	97		

Statistical analyses

Statistical analysis title	Difference postoperative delirium
Comparison groups	Test group v Comparison group

Number of subjects included in analysis	195
Analysis specification	Pre-specified
Analysis type	other[1]
P-value	< 0.05
Method	Wilcoxon (Mann-Whitney)

Notes:

[1] - The standard test for categorical variables with a large sample size will be analysed by the Chi-square test. Fisher's test will be executed in test situations, when the cell frequence in a contingency table is small, typically less than 5. In addition, differences of test scores between test and comparison group for the employed tests will be reported and analysed statistically using the Mann-Withney u-test. Test scores represent data on the ordinal scale.

Secondary: Plasma osmolality

End point title	Plasma osmolality

End point description:

End point type	Secondary

End point timeframe:

Plasma osmolality is measured intraoperatively and twice postoperatively (day 1 and day 3).

End point values	Test group	Comparison group		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	98	97		
Units: mmol				
number (not applicable)	98	97		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From the time a patient receives the first dose of study treatment until 24 hours thereafter.	
Assessment type	Systematic

Dictionary used	
Dictionary name	CTCAE
Dictionary version	5

Reporting groups	
Reporting group title	Test group
Reporting group description:	
Cardiac surgical patients requiring cardiopulmonary bypass randomised to: Priming of the heart-lung machine: Ringer-Acetate 1000 ml + Mannitol 60 g + Sodium Chloride 160 mmol + Heparin 10 000 IU	
Reporting group title	Comparison group
Reporting group description:	
Cardiac surgical patients requiring cardiopulmonary bypass randomised to: Priming of the heart-lung machine: Ringer-Acetate 1400 ml + Heparin 10 000 IU	

Serious adverse events	Test group	Comparison group	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 100 (0.00%)	0 / 100 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Test group	Comparison group	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	5 / 100 (5.00%)	2 / 100 (2.00%)	
Investigations			
Creatine urine increased			
subjects affected / exposed	1 / 100 (1.00%)	1 / 100 (1.00%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
other	Additional description: Increasing pressure drop, membrane oxygenator		
subjects affected / exposed	2 / 100 (2.00%)	1 / 100 (1.00%)	
occurrences (all)	2	1	
Vascular disorders			

Unstable blood pressure subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 100 (0.00%) 0	
Nervous system disorders Encephalopathy subjects affected / exposed occurrences (all)	1 / 100 (1.00%) 1	0 / 100 (0.00%) 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