Clinical trial results:
Continuous hyperosomolar therapy for traumatic brain-injured Patients Study protocol for a multicenter randomized open-label trial with blinded adjudication of primary outcome

Summary

EudraCT number	2017-000073-36
Trial protocol	FR
Global end of trial date	05 March 2020

Results information

Result version number	v1 (current)
This version publication date	20 September 2022
First version publication date	20 September 2022

Trial information

Trial identification

Sponsor protocol code	RC16_0474

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03143751
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	CHU Nantes
Sponsor organisation address	5 allée de l'île Gloriette, Nantes, France, 44093
Public contact	Direction recherche , CHU de Nantes, CHU de Nantes , 0033 0253482430, patrice.chauveau@chu-nantes.fr
Scientific contact	Direction recherche , CHU de Nantes, CHU de Nantes , 0033 0253482430, patrice.chauveau@chu-nantes.fr

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	14 September 2021
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	05 March 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To demonstrate the effectiveness of continuous intravenous osmotherapy with hypertonic saline to improve the neurological recovery of patients with traumatic brain injury.

Protection of trial subjects:

Monitoring of the blood ionogram during the administration of the treatment.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	31 October 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	France: 370
Worldwide total number of subjects	370
EEA total number of subjects	370

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)	303
From 65 to 84 years	67
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment took place within the anesthesia and resuscitation departments of 10 hospitals in France between 10/31/2017 and 03/05/2020.
The screening was carried out by the emergency physician investigators or anesthetist-resuscitators or medical resuscitators caring for patients with cranial trauma in the initial phase.

Pre-assignment

Screening details:

Inclusion Criteria:
18-80 years old
Moderate to severe traumatic brain injury defined as the association of a Coma Glasgow Scale ≤ 12 together with a traumatic abnormal brain CT-scan
Time to inclusion inferior to 24 hours
Exclusion Criteria:
Coma Glasgow Scale of 3 and fixed dilated pupils
associated cervical spine injury

Pre-assignment period milestones

Number of subjects started	370
Number of subjects completed	370

Period 1

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

Blinding implementation details:

Single-blind (patient) with blind evaluation of the primary endpoint

Arms

Are arms mutually exclusive?	Yes
Arm title	Experimental: Continuous hyperosmolar therapy

Arm description:

Standard cares plus continuous hyperosmolar therapy (NaCl20%)
Early intravenous administration (<24 hours after traumatic brain injury) of NaCl20% for a minimal duration of 48 hours (continued for as long as is necessary to prevent intracranial hypertension)

Arm type	Experimental
Investigational medicinal product name	sodium chloride 20%
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection/infusion
Routes of administration	Intravenous drip use

Dosage and administration details:

Early intravenous administration (<24 hours after traumatic brain injury) of NaCl20% for a minimal duration of 48 hours (continued for as long as is necessary to prevent intracranial hypertension)

1-hour bolus (15 g if Na+ < 145 mmol/L; 7.5 g if 145 < Na+ < 150 mmol/L; or no bolus) followed by 1 g/hour as long as Na+< 150 mmol/L, reduced to 0.5 g/L if 150 < Na+ < 155 mmol/L, Discontinuation when 155 mmol/L<Na+

Arm title	Control: No Intervention

Arm description:	
Standard cares alone.	
Arm type	No intervention
No investigational medicinal product assigned in this arm	

Notes:

[1] - The number of roles blinded appears inconsistent with a single blinded trial. It is expected that there will be one role blinded in a single blind trial.

Justification: The applied protocol planned consisted to evaluate Glasgow Outcome Scale Extended at 3 and 6 months by a single trained research associate blinded to the treatment received in intensive care.

Number of subjects in period 1	Experimental: Continuous hyperosmolar therapy	Control: No Intervention
Started	185	185
Completed	181	178
Not completed	4	7
Lost to follow-up	4	4
Protocol deviation	-	3

Baseline characteristics

Reporting groups	
Reporting group title	Experimental: Continuous hyperosmolar therapy
Reporting group description:	
Standard cares plus continuous hyperosmolar therapy (NaCl20%) Early intravenous administration (<24 hours after traumatic brain injury) of NaCl20% for a minimal duration of 48 hours (continued for as long as is necessary to prevent intracranial hypertension)	
Reporting group title	Control: No Intervention
Reporting group description:	
Standard cares alone.	

Reporting group values	Experimental: Continuous hyperosmolar therapy	Control: No Intervention	Total
Number of subjects	185	185	370
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 Units: years			
median	46	43	
inter-quartile range (Q1-Q3)	27 to 60	27 to 59	-
Gender categorical Units: Subjects			
Female	40	37	77
Male	145	148	293

End points

End points reporting groups

Reporting group title	Experimental: Continuous hyperosmolar therapy
Reporting group description:	
Standard cares plus continuous hyperosmolar therapy (NaCl20%) Early intravenous administration (<24 hours after traumatic brain injury) of NaCl20% for a minimal duration of 48 hours (continued for as long as is necessary to prevent intracranial hypertension)	
Reporting group title	Control: No Intervention
Reporting group description:	
Standard cares alone.	
Subject analysis set title	Primary outcome
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
Analysis on 359 patients who achieved the Primary outome at 6 months among 370 randomized patients	

Primary: Score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months

End point title	Score on the Extended Glasgow Outcome Scale (GOS-E) at 6 months
End point description:	
End point type	Primary
End point timeframe:	
At 6 months	

End point values	Experimental: Continuous hyperosmolar therapy	Control: No Intervention	Primary outcome	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	181	178	359	
Units: Patients				
Dead	29	37	66	
Vegetative state	1	3	4	
Lower severe disavility	35	27	62	
Upper severe disavility	28	21	49	
Lower moderate disavility	29	27	56	
Upper moderate disavility	27	29	56	
Lower good recovery	23	18	41	
Upper good recovery	9	16	25	

Statistical analyses

Statistical analysis title	Adjusted ordinal logistic regression model
Comparison groups	Experimental: Continuous hyperosmolar therapy v Control: No Intervention

Number of subjects included in analysis	359
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.92
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.02
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.71
upper limit	1.47

Adverse events

Adverse events information	
Timeframe for reporting adverse events: 48 hours after the end of the treatment administration	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups	
Reporting group title	Intervention
Reporting group description: -	
Reporting group title	Control
Reporting group description: -	

Serious adverse events	Intervention	Control	
Total subjects affected by serious adverse events			
subjects affected / exposed	55 / 185 (29.73%)	47 / 185 (25.41%)	
number of deaths (all causes)	29	37	
number of deaths resulting from adverse events			
Injury, poisoning and procedural complications			
Dose calculation error			
subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Drug monitoring procedure incorrectly performed			
subjects affected / exposed	3 / 185 (1.62%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Extradural haematoma			
subjects affected / exposed	3 / 185 (1.62%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Incorrect product administration duration			

subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product administration error			
subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product selection error			
subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Subdural haematoma			
subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Underdose			
subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Cardio-respiratory arrest			
subjects affected / exposed	0 / 185 (0.00%)	2 / 185 (1.08%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	25 / 185 (13.51%)	36 / 185 (19.46%)	
occurrences causally related to treatment / all	0 / 30	0 / 37	
deaths causally related to treatment / all	0 / 10	0 / 18	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	

Respiratory, thoracic and mediastinal disorders			
Respiratory disorder			
subjects affected / exposed	7 / 185 (3.78%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 7	0 / 1	
deaths causally related to treatment / all	0 / 3	0 / 0	
Endocrine disorders			
Diabetes insipidus			
subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Infection			
subjects affected / exposed	6 / 185 (3.24%)	4 / 185 (2.16%)	
occurrences causally related to treatment / all	0 / 7	0 / 4	
deaths causally related to treatment / all	0 / 0	0 / 1	
Metabolism and nutrition disorders			
Metabolic disorder			
subjects affected / exposed	23 / 185 (12.43%)	9 / 185 (4.86%)	
occurrences causally related to treatment / all	17 / 23	0 / 9	
deaths causally related to treatment / all	0 / 1	0 / 0	

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

Non-serious adverse events	Intervention	Control	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	158 / 185 (85.41%)	162 / 185 (87.57%)	
Investigations			
Liver function test abnormal			
subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences (all)	0	1	
Injury, poisoning and procedural complications			
Extradural haematoma			
subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences (all)	1	0	
Head injury			

subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences (all)	0	1	
Incorrect product administration duration			
subjects affected / exposed	2 / 185 (1.08%)	0 / 185 (0.00%)	
occurrences (all)	2	0	
Unintentional medical device removal			
subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences (all)	1	0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 185 (0.54%)	1 / 185 (0.54%)	
occurrences (all)	1	1	
Hypertension			
subjects affected / exposed	1 / 185 (0.54%)	0 / 185 (0.00%)	
occurrences (all)	1	0	
Hypotension			
subjects affected / exposed	1 / 185 (0.54%)	6 / 185 (3.24%)	
occurrences (all)	1	6	
Jugular vein thrombosis			
subjects affected / exposed	4 / 185 (2.16%)	7 / 185 (3.78%)	
occurrences (all)	4	7	
Cardiac disorders			
Cardiac disorder			
subjects affected / exposed	4 / 185 (2.16%)	0 / 185 (0.00%)	
occurrences (all)	4	0	
Nervous system disorders			
Nervous system disorder			
subjects affected / exposed	35 / 185 (18.92%)	26 / 185 (14.05%)	
occurrences (all)	35	26	
General disorders and administration site conditions			
Withdrawal syndrome			
subjects affected / exposed	0 / 185 (0.00%)	1 / 185 (0.54%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			

Respiratory disorder subjects affected / exposed occurrences (all)	5 / 185 (2.70%) 5	5 / 185 (2.70%) 5	
Skin and subcutaneous tissue disorders Acute generalised exanthematous pustulosis subjects affected / exposed occurrences (all)	0 / 185 (0.00%) 0	1 / 185 (0.54%) 1	
Renal and urinary disorders Renal disorder subjects affected / exposed occurrences (all)	3 / 185 (1.62%) 3	12 / 185 (6.49%) 12	
Endocrine disorders Endocrine disorder subjects affected / exposed occurrences (all)	5 / 185 (2.70%) 5	14 / 185 (7.57%) 14	
Infections and infestations Infection subjects affected / exposed occurrences (all)	92 / 185 (49.73%) 92	89 / 185 (48.11%) 89	
Metabolism and nutrition disorders Metabolic disorder subjects affected / exposed occurrences (all)	6 / 185 (3.24%) 6	5 / 185 (2.70%) 5	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
21 December 2017	Addition of an ancillary study (quality of life questionnaire for a relative of the patient); change of scale for measuring autonomy: MIF replaced by Katz's ADL.
27 June 2019	Change in the protocol in order to collect additional data not initially planned: - assessment of the risk of hyperchloremia (hyperchloremic acidosis): chloremia, potassium and pH values - to evaluate the impact of osmotherapy on cerebral oxygenation: the quantity of oxygen in the cerebral tissue is measured by a PtiO2 probe and the data collected makes it possible to study the treatment on this neurological evaluation criterion. - Clarification of the evaluation of the frequency of renal failure (Stages 2 or 3 of the KDIGO scale): according to the values of creatinine, diuresis and weight.

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/34032829