ISRCTN17097163 https://doi.org/10.1186/ISRCTN17097163

Can Cerebrolysin improve recovery after traumatic brain injury?

Submission date
05/12/2018

Recruitment status
No longer recruiting

Registration date
21/12/2018

Overall study status
Completed

Last Edited
04/02/2026

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[X] Results
[_] Individual participant data

Plain English summary of protocol

Background and study aims
Traumatic brain injury (TBI) is one of the leading causes of injury-related death. In the United States alone, an estimated 1.7 million people sustain a TBI each year, and approximately 5.3 million people live with a TBI-related disability. The direct medical costs and indirect costs such as lost productivity of TBIs totaled an estimated $76.5 billion in the U.S. in the year 2000. Improving the limited treatment options for this condition remains challenging. However, recent reports from interdisciplinary working groups (consisting primarily of neurologists, neurosurgeons, neuropsychologists, and biostatisticians) have stated that to improve TBI treatment, important methodological lessons from the past must be taken into account in future clinical research. An evaluation of the neuroprotection intervention studies conducted over the last 30 years has indicated that a limited understanding of the underlying biological concepts and methodological design flaws are the major reasons for the failure of pharmacological agents to demonstrate efficacy. Cerebrolysin is a parenterally-administered neuro-peptide preparation that acts in a manner similar to endogenous neurotrophic factors. Cerebrolysin has a favorable adverse effect profile, and several meta-analyses have suggested that Cerebrolysin is beneficial as a dementia treatment. This trial is a randomized, double-blind, placebo-controlled, single-center trial of the effects of Cerebrolysin on neuroprotection and neurorecovery after TBI using a multidimensional ensemble of outcome scales. The trial will be the first TBI trial with a 'true' multidimensional approach based on full outcome scales, while avoiding prior weaknesses, such as loss of information through "dichotomization," or unrealistic assumptions such as "normal distribution."

Who can participate?
Adults over the age of 18 a diagnosis of traumatic brain injury (TBI) and a Glasgow Coma Scale (GCS) score of 7-12 at the time of hospital admission at the study centre in Cluj-Napoca, Romania.

What does the study involve?
Participants are invited to join this study during inpatient admission for traumatic brain injury. After informing patients about study procedures, benefits and potential risks, consent in sought. All participants included in the study must pass the screening criteria and baseline evaluations. Individuals are then randomly allocated to one of two groups. The first group is administered a placebo (NaCl) version of the drug, while the second group receives Cerebrolysin, a mixture of

peptides purified from pig brains, including (and not limited to) brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and ciliary neurotrophic factor (CNTF). This study is performed under double-blind conditions to keep investigators, other study personnel and patients blinded to treatment allocation. Cerebrolysin is an amber-colored solution; therefore, coloured infusion lines will be used for drug administration. Study enrolment lasts until the estimated necessary sample size (n=140) is achieved. Participants are assessed using a battery of cognitive, emotional and serologic evaluations at days 10, 30 and 90 after the time of traumatic brain injury. Results are analysed to establish safety and efficacy of the intervention. No further follow-up is performed.

What are the possible benefits and risks of participating?
Potential benefits of Cerebrolysin administration in patients with TBI are improved functional recovery, decreased mortality rate and increased favourable outcome. The main risk for patients is developing adverse events (AE). The severity of AEs and the causality to study medication is carefully assessed in order to establish a detailed safety profile of the intervention. Due to inpatient admission, appropriate care for adverse effects is promptly available.

Where is the study run from?
The CAPTAIN-RO is a single centre trial run from Cluj-Napoca, Romania.

When has the study started and how long is it expected to run for?
April 2013 to December 2017

Who is funding the study?
The Society for the Study of Neuroprotection and Neuroplasticity (SSNN) (Romania)

Who is the main contact?
1. Prof. Dr. Dafin Fior Muresanu
dafinm@ssnn.ro
2. Stefan Strilciuc, MPH
stefan.strilciuc@ssnn.ro

Contact information

Type(s)
Scientific

Contact name
Prof Dafin Muresanu

ORCID ID
https://orcid.org/0000-0002-9536-1153

Contact details
No. 37 Mircea Eliade Street
Cluj-Napoca
Romania
400364
+40740066761
dafinm@ssnn.ro

Additional identifiers

Protocol serial number
N/A

Study information

Scientific Title
Cerebrolysin trial in neuroprotection and neurorecovery after traumatic brain injury

Study objectives
Cerebrolysin is superior to placebo on general and neurocognitive outcomes after traumatic brain injury.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy, Cluj-Napoca, Romania, 20/03/2013, ref: 714/07.03.2013. Amended 09/02/2016 (ref: 27/09/02/2016) and 10.03.2017 (ref:115/10/03/2017).

Study design
Randomized double-blind controlled single-center trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Traumatic brain injury (TBI) with Glasgow Coma Scale (GCS) scores between 7 and 12.

Interventions
The synopsis of the study is organised in 4 visits.
1. Screening and baseline
2. Day 10 evaluation
3. Day 30 evaluation
4. Day 90 evaluation

No follow-up was performed after the 90-day evaluation. The study arms were administered the following treatment courses:

Control group
1. Days 1-10: Placebo IV
2. Days 31-40: Placebo IV
3. Days 61-70: Placebo IV
Placebo: 250 ml 0.9% NaCl.

Treatment group
1. Days 1-10: 50 ml Cerebrolysin IV
2. Days 31-40:10 ml Cerebrolysin IV
3. Days 61-70: 10 ml Cerebrolysin IV
Cerebrolysin - diluted in 0.9% NaCl to a total volume of 250 ml.

Randomisation, Blinding and Unblinding
This study will be performed under double-blind conditions to keep investigators, other study personnel and patients blinded to treatment allocation. Cerebrolysin is an amber-colored solution. Therefore, colored infusion lines will be used for drug administration.

Patients meeting in- and exclusion criteria will obtain a random number corresponding to the random list generated in advance by a biometrician selected by the sponsor. Patients will be randomly allocated to the study groups in a 3:4 ratio.

Production and Maintainance of Randomization Codes
Each presenting patient who qualifies for entry into the active treatment period is assigned a unique randomization number (patient number). This number is the next available randomization number in ascending order from 001 to e.g., 999 of a predefined randomization plan and identifies the treatment assigned to a unique patient in a double-blind way.

Patients are allocated to one of both treatment groups in a 3:4 ratio.

A balanced random code list is prepared using the random permuted block scheme. In accordance with the ICH Biostatistics Guideline, the block size is intentionally not given in the study protocol (ICH E9 § 2.3.2, “Investigators and other relevant staff should generally be blind to the block length”).

The sealed random code list and the sets of sealed envelopes are prepared using the validated program RANCODE in a validated working environment at idv Data Analysis and Study Planning, Gauting, Germany.
Sealed emergency envelopes will be provided to the Study Safety Officer (SSO) as well as to the Principle Investigator and the Study Nurse responsible for the preparation of the study medication at each study site.

Blinded Preparation of Study Medication
The person who prepares the infusion at the study center will be independent of all other study specific procedures, in particular any safety or efficacy assessments and the study nurse is not allowed to disclose any information about treatment allocation.

The randomization envelope will be opened by the nurse at the time when the patient’s first ready-to-use-infusion is being prepared. The double-blind study medication labels of the ready-to-use-infusion will identify only the unique randomization number which is the same as the patient number.

Breaking the Randomization Codes / Unblinding
The Principle Investigator will receive a sealed envelope for each patient containing information as to the identity of the treatment dispensed. The randomization code for a patient may only be broken by the principal investigator for the following reasons:
1. In the event of an SAE that the investigator feels cannot be treated without knowing the

identity of the study medication
2. If other reasonable suspicion of harm to the patient exist that requires knowledge of the study treatment

Every effort must be made to inform the designated Study Safety Officer prior to breaking the blind, or if it is an emergency, as soon as possible thereafter. Should unblinding be necessary, the randomization/emergency envelopes are dated (date, hour) and signed by the person who has opened the envelope and the investigator must provide a written explanation on the patient' s CRF.

The whole study will be unblinded after closure of the database and finalization of the statistical analysis plan.

Intervention Type
Drug

Phase
Phase III/IV

Drug/device/biological/vaccine name(s)
Cerebrolysin

Primary outcome(s)
1. Cognitive function assessed using PSI (Processing Speed Index, Wechsler adult intelligence scale – third edition) at days 10, 30, 90.
2. Cognitive function assessed using Stroop Color-Word Test – Victoria Version (VST) (Marcus, 1976) at days 10, 30, 90.
3. Cognitive function assessed using Color Trails Test (Posch, 2005) at days 30, 90.
4. Cognitive function assessed using Digit Span (Wechsler adult intelligence scale – third edition (Wechsler, 1997) at days 30, 90.
5. Cognitive function assessed using Early Rehabilitation Barthel Index (Schoenle, 1995) at days 10, 30, 90.
6. Cognitive function assessed using Finger Tapping Test (Huang, 2008) at days 30, 90.
7. Cognitive function assessed using Mini-Mental State Examination (MMSE) (Folstein, 1975) at days 10, 30, 90.
8. Emotional status assessed using Hospital Anxiety and Depression Scale (Zigmond, 1983) at days 30, 90.
9. Cognitive function assessed using Glasgow Outcome Scale Extended (GOS-E) (Wilson,1998) at days 10, 30, 90.

Key secondary outcome(s))
1. Serum biomarkers assessed using NSE, S-100 B and APOE ε2-4 levels at baseline.

Completion date
01/04/2018

Eligibility

Key inclusion criteria
1. Diagnosis of TBI and a GCS score of 7-12 at the time of hospital admission. Pre-hospital intubation/sedation/paralysis is accepted if the GCS score has been assessed before intubation

/sedation/paralyses by trained personnel.
2. Pre-treatment GCS score of 7-12. If intubation/sedation/paralysis occurs after hospital admission, the pre-treatment GCS score has been assessed before intubation/sedation /paralyses.
3. Isolated TBI only (abbreviated injury score (AIS) in other body regions of ≤2)
4. CT (Marshal classification) I to VI (from diffuse injury to non-evacuated mass lesion)
5. Pre-Trauma Karnofsky Index = 100. If no corresponding information is available before the start of treatment (e.g., patient is unconscious or not able to communicate) and no information is retrieved within 24 hours after the start of treatment, the patient stays in the study. If no information is available before the start of treatment and a violation of the Karnofsky Index is detected within 24 hours after the start of treatment, the patient is withdrawn from the study, and the treatment medication is stopped.
6. Aged 18-80 years
7. Able to provide written informed consent to enrollment
8. Willing and able to comply with the protocol requirements for the duration of the study
9. Women of child-bearing potential with a negative urine pregnancy test who are willing to practice an acceptable method of birth control
10. Time to needle for study medication should be within 4 hours
11. Patients were able to speak, read and write before the accident. If no corresponding information is available before the start of treatment (e.g., patient is unconscious or not able to communicate) and if no information is retrieved within 24 hours after the start of treatment, the patient should remain in the study. If no information is available before the start of treatment and if a violation of this inclusion criterion is detected within 24 hours after the start of treatment, the patient should be withdrawn from the study, and the treatment medication should be stopped.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Total final enrolment
142

Key exclusion criteria
1. Patients with polytrauma (AIS score in other body regions of >2)
2. Patients with spinal cord injury
3. History of intracranial interventionor ischemic or hemorrhagic stroke

4. Existence of psychiatric disorders or neurodegenerative diseases
5. Patients who in the investigator’s opinion would not comply with study procedures
6. Patients with a history of epileptic seizure
7. Use of concomitant neuroprotective treatment or cholinesterase inhibitors for previous cognitive treatment
8. Persons who are under chronic treatment with cortisone, Ca+-channel blockers, antidepressants, antipsychotic drugs or nootropic molecules
9. Significant or unstable medical, systemic or logistical condition that affects the subject’s ability to give informed consent or to complete the study procedures

Date of first enrolment
24/04/2013

Date of final enrolment
28/12/2017

Locations

Countries of recruitment
Romania

Study participating centre
Emergency Clinical County Hospital Cluj-Napoca, Neurology Clinic and Neurosurgery Clinic
3-5 Clinicilor Street
Cluj-Napoca
Romania
400000

Sponsor information

Organisation
EN: The foundation for the study of neuroscience and reuroregeneration (RO: Fundatia pentru Studiul Nanoneurostiintelor si Neuroregenerarii)

Funder(s)

Funder type
Research organisation

Funder Name
EN: The foundation for the study of neuroscience and neuroregeneration (RO: Fundatia pentru Studiul Nanoneurostiintelor si Neuroregenerarii)

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	01/05/2020	28/02/2020	Yes	No
Basic results		06/03/2020	06/03/2020	No	No
Other publications	Cost-effectiveness of Cerebrolysin as an add-on treatment for neurorecovery after traumatic brain injury	05/05/2025	04/02/2026	Yes	No
Protocol file			02/07/2024	No	No