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Can treatment with Cerebrolysin and magnetic stimulation of the brain improve recovery after traumatic brain injury?

Submission date
11/02/2019

Recruitment status
No longer recruiting

Registration date
19/02/2019

Overall study status
Completed

Last Edited
19/08/2024

Condition category
Injury, Occupational Diseases, Poisoning

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

Plain English summary of protocol

Background and study aims
Traumatic brain injury (TBI) represents a major cause of injury-related death and disability, especially in the young population. Long term outcome includes many possible complications, including impaired thinking ability and emotional, behavioral, and personality disturbances. This study is combining Cerebrolysin (CRB) treatment with repetitive transcranial magnetic stimulation (rTMS), in order to improve health outcomes in patients with moderate-severe TBI.

Who can participate?
Adults between 18 and 70-years old with a traumatic brain injury onset 30 days prior to screening.

What does the study involve?
Participants are invited to join this study at 30 days post TBI. After informing patients about study procedures, benefits and potential risks, consent is sought. All participants included in the study must pass the screening criteria and baseline evaluations. Individuals are then randomly allocated to one of three groups. The first group is administered Cerebrolysin and repetitive transcranial magnetic stimulation (rTMS), the second group receives Cerebrolysin and sham rTMS, while the third group receives a placebo (saline solution) and sham rTMS.

What are the possible benefits and risks of participating?
Potential benefit of Cerebrolysin and repetitive transcranial magnetic stimulation administration in patients with TBI is improved mental and physical health. 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.

Where is the study run from?
The CAPTAIN-rTMS 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 2018 to February 2022

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
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
FSNN040418

Study information

Scientific Title
Cerebrolysin and Repetitive Transcranial Magnetic Stimulation (Rtms) in Patients with Traumatic Brain Injury

Acronym
CAPTAIN-rTMS

Study objectives
Combining the repetitive transcranial magnetic stimulation with Cerebrolysin in cognitive rehabilitation of patients with traumatic brain injuries will improve cognitive function better than either treatment alone or placebo treatment.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 01/02/2018, Ethics Committee of the Iuliu Hatieganu University of Medicine and Pharmacy (8 Babeş Street, 400012 Cluj-Napoca, Romania; +40-264-597-256; contact@umfcluj.ro), ref: 2/08.01.2018. Amended 171/02.04.2018 (ref: 133/15.03.2018)

Amended 30/05/2019 (ref. 118/23.04.2019)

Study design
Monocentric randomized double-blind phase II study

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Traumatic Brain Injury (TBI) onset 30 days prior to screening

Interventions
The synopsis of the study is organised in 3 visits:
1. Screening and Baseline - Study Day 30
2. Visit 1 - Study Day 101
3. Visit 2 - Study Day 180

No follow-up was performed after the 180-day evaluation. The study arms were administered the following treatment courses:

1. Treatment Group CRB + rTMS:
Days 31-40: 30 ml Cerebrolysin IV + rTMS
Days 61-70: 30 ml Cerebrolysin IV + rTMS
Days 91-100: 30 ml Cerebrolysin IV + rTMS
Cerebrolysin - diluted in 0.9% saline solution up to 250 ml
rTMS - stimulation parameters for left DLPFC: 10 Hz, 1,200 stimuli/day, intensity of 120% of resting motor threshold.

2. Treatment Group CRB + sham rTMS:
Days 31-40: 30 ml Cerebrolysin IV + sham rTMS
Days 61-70: 30 ml Cerebrolysin IV + sham rTMS
Days 91-100: 30 ml Cerebrolysin IV + sham rTMS
Cerebrolysin - diluted in 0.9% saline solution up to 250 ml

3. Treatment Group placebo + sham rTMS:
Days 31-40: Placebo IV + sham rTMS
Days 61-70: Placebo IV + sham rTMS
Days 91-100: Placebo IV + sham rTMS
Placebo: 250 ml 0.9% saline solution

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 inclusion and exclusion criteria will obtain a random number corresponding to the random list generated in advance by a biometrician selected by the sponsor.
A set of envelopes for each patient enrolled should be distributed to the study nurse preparing the ready-to-use-infusion solution. These nurses are only responsible for the preparation and administration of infusion solutions, and they should not be involved in any further study-related procedures. This person should not be allowed to disclose any information about treatment allocation. A treatment envelope should not be opened until the patient's first ready-to-use-infusion has been prepared.
Sham stimulation will be performed with a sham-coil (MCF-P-B 65, Magventure) which has a mechanical outline and sound level identical to MCF-B65, and also provides the same level of cutaneous discofort and muscle twiching as real stimulation. The rTMS (both sham and real) administration will be provided by two rTMS technicians which will not be involved in any further study-related procedures and will not be allowed to disclose any information about treatment procedure.

On opening, the randomization/emergency envelopes are dated (date, hour) and signed by the person who has opened the envelope. The Investigator should promptly document and explain to the Sponsor any premature unblinding of the Investigational Product(s).

The whole study will be unblinded after closure of the database and determination of the analysis populations.

Intervention Type
Drug

Phase
Phase II

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

Primary outcome(s)
1. Cognitive function assessed using Stroop Color-Word Test (Stroop, 1935) at days 30, 101, 180
2. Cognitive function assessed using Montreal Cognitive Assessment (MoCA) (Nasreddine, 2005) at days 30, 101, 180
3. Cognitive function assessed using PSI (Processing Speed Index, Wechsler adult intelligence scale – third edition) (Wechsler, 1997) at days 30, 101, 180
4. Cognitive function assessed using Digit Span (Wechsler adult intelligence scale – third edition) (Wechsler, 1997) at days 30, 101, 180
5. Cognitive function assessed using Trail Making Test (Reitan, 1958) at days 30, 101, 180
6. Emotional status assessed using Hamilton Anxiety Rating Scale (Hamilton, 1959) at days 30, 101, 180
7. Emotional status assessed using Hamilton Rating Scale for Depression (Hamilton, 1960) at days 30, 101, 180
8. Cognitive function assessed using One Touch Stockings of Cambridge at days 30, 101, 180
9. Cognitive function assessed using The Multitasking Test at days 30, 101, 180
10. Cognitive function assessed using Reaction Time at days 30, 101, 180

Key secondary outcome(s))
1. Eye movements assessed using a Tobii Pro TX300 eye-tracking device and analyzed using Tobii Studio software at 30, 101 and 180 days.
2. Brain electrical activity assessed using electoencephalography (EEG) and analyzed quantitatively using BrainAnalyzer software at 30, 101 and 180 days.
3. Adverse events of magnetic stimulation of the brain recorded using a tailored safety report form based on patient self-reports during the entire duration of the trial.

Completion date
28/02/2022

Eligibility

Key inclusion criteria
1. Traumatic brain injury onset 30 days prior to screening
2. CT/MRI – focal and/or diffuse lesions
3. Age: 18-70 years, inclusive (updated 28/02/2020: 18-80 years, inclusive)
4. Pre-Trauma Karnofsky Index 100
5. Willing and able to comply with the protocol requirements for the duration of the study

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit

18 years

Upper age limit
80 years

Sex
All

Total final enrolment
93

Key exclusion criteria
1. Metal implant in the head or within the stimulation area
2. Medical implanted devices (cardiac pacemaker, cochlea implant or medication pumps)
3. History of intracranial interventions as well as ischemic or hemorrhagic stroke
4. Evidence of pre-existing major health problems (e.g., cancer, haematological, renal, hepatic, or coronary disease, psychiatric disorder, diabetes, myocardial infarction or other known heart diseases, disabling or musculoskeletal problems like rheumatoid arthritis, epilepsy, evidence of degenerative or inflammatory diseases affecting nervous system [e.g., Alzheimer, Parkinson]). Patients with well-controlled diabetes and hypertension can be included if there is no evidence of secondary damage to major organs.
5. Any neurological or non-neurological condition independent from TBI that might influence the functional outcome or other efficacy outcome measures.
6. Injury of writing hand influencing cognitive or other outcome measures, in the investigator's judgment.
7. Clear clinical signs of intoxication influencing the evaluation, in the investigator's judgment.
8. Major drug dependency including alcohol, in the investigator's judgment.
9. Chronic treatment with steroids, Ca2+-channel blockers or major anticoagulants (e.g., warfarin and other coumarin derivates), monoamine oxidase inhibitors, antipsychotic drugs or nootropic molecules.
10. Patient with penetrating brain injury.
11. Females who are pregnant or lactating.
12. Females who are of child bearing potential and not taking adequate contraceptive precautions are excluded from the trial. Females of child bearing potential taking acceptable contraceptive precautions can be included. A highly effective method of birth control and one which is acceptable for this study, is defined as those which result in a low failure rate (i.e. less than 1% per year) when used consistently and correctly such as implants, injectables, combined oral contraceptives, some IUDs, sexual abstinence or vasectomised partner.

Date of first enrolment
19/03/2018

Date of final enrolment
30/09/2021

Locations

Countries of recruitment
Romania

Study participating centre
“RoNeuro” Institute for Neurological Research and Diagnostic
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Sponsor information

Organisation
EN: The foundation for the study of neuroscience and neuroregeneration (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 current data sharing plans for this study are unknown and will be available at a later date

IPD sharing plan summary
Data sharing statement to be made available at a later date

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		08/06/2023	31/08/2023	Yes	No
Results article		03/03/2024	19/07/2024	Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 1.1	07/05/2018	31/08/2023	No	No
Statistical Analysis Plan	version 1.0		19/08/2024	No	No