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Can adding cerebrolysin early to clot-dissolving stroke treatment reduce the risk of brain bleeding?

Submission date
01/02/2021

Recruitment status
No longer recruiting

Registration date
16/02/2021

Overall study status
Completed

Last Edited
24/03/2025

Condition category
Circulatory System

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

Plain English Summary

Background and study aims
Ischemic stroke is a type of stroke caused by a blockage in an artery that supplies blood to the brain. This blockage reduces blood flow and oxygen, leading to damage or death of brain cells. It is also known as brain ischemia or cerebral ischemia. Intravenous thrombolysis (IVT) is the standard treatment for patients with acute ischemic stroke. It works by dissolving blood clots, improving blood flow, and reducing the risk of damage to tissues and organs. IVT can significantly improve recovery after a stroke. However, some patients may experience complications in the damaged brain tissue after receiving thrombolysis, which can worsen outcomes. Cerebrolysin, a neuroprotective medication, has shown potential benefits in protecting brain cells and supporting recovery. It is approved in Russia and some other countries as an additional treatment for acute ischemic stroke. This study aims to test whether Cerebrolysin, when used alongside IVT, can reduce the risk of complications and improve outcomes for patients with ischemic stroke.

Who can participate?
Adult patients with acute ischemic stroke who arrive at participating hospitals within 4.5 hours after the stroke onset and who are eligible for intravenous thrombolytic therapy.

What does the study involve?
After signing an informed consent form, participants are randomly assigned to either the treatment group (case group) or the control group.
• Both groups: All participants will receive standard care, including IVT.
• Case group: Participants will also receive daily intravenous infusions of Cerebrolysin for 14 consecutive days.
All other treatments and diagnostic procedures will follow current clinical guidelines. In some hospitals, participants from both groups may undergo advanced brain imaging if the technology is available.

What are the possible benefits and risks of participating?
Possible benefits:

• You may receive a potentially more effective treatment before it becomes widely available.
• In some hospitals, you may have access to advanced brain imaging during your care.
• You could play a more active role in managing your health.
• Your participation may help improve stroke treatments for others in the future.
Possible risks:
• The new treatment may cause side effects or discomfort.
• It may not be more effective than the standard treatment.
• If you are assigned to the control group, you will only receive the standard treatment.

Where is the study run from?
The study is being conducted at participating hospitals. For more details, please refer to the full list of locations or contact the main investigator.

When is the study starting and how long is it expected to run for?
April 2018 to November 2020

Who is funding the study?
Investigator initiated and funded

Who is the main contact?
Mikhail Kalinin, ninilak@gmail.com

Contact information

Type(s)
Scientific

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Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
C2XX1A-2018

Study information

Scientific Title
Cerebrolysin as an Early add-on to Reperfusion therapy: risk of hemorrhagic transformation after ischemic stroke (CEREHETIS). A prospective, randomized, multicenter pilot study

Acronym
CEREHETIS

Study hypothesis
Cerebrolysin reduces risk of hemorrhagic transformation when introduced as early add-on to reperfusion therapy for ischemic stroke.

Ethics approval required
Ethics approval required

Ethics approval(s)
Approved 24/04/2018, Ethics Committee of the Interregional Clinical Diagnostic Center (12A, Karbyshev str., Kazan, 420101, Russian Federation; +7 (843) 291-10-16; icdc@icdc.ru), ref: protocol #81

Study design
Prospective randomized active-control multicenter trial in parallel groups

Primary study design
Interventional

Secondary study design

Randomised parallel trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet

Condition
Ischemic stroke

Interventions
Current interventions as of 25/11/2024:
Participants will be randomized in a 1:2 ratio into either the case or control group using a computer-generated randomization process.
• Control group: Participants will receive intravenous thrombolysis (IVT) with recombinant tissue plasminogen activator (alteplase, 0.9 mg/kg).
• Case group: Participants will receive IVT with alteplase (0.9 mg/kg) in addition to 30 mL of Cerebrolysin diluted in 100 mL of normal saline, administered simultaneously via a separate intravenous cubital line over 20 minutes. Daily infusions of Cerebrolysin will continue for 14 consecutive days.
Standard care, as per current clinical guidelines, will be permitted for both groups.

Previous interventions:
Randomization in a 1:2 ratio into case or control group by using a random number generating software.
Control group: Intravenous thrombolytic therapy (IV TLT) with recombinant tissue plasminogen activator (alteplase, 0.9 mg/kg).
Case group: IV TLT + at the same time Cerebrolysin 30 mL diluted in 100 mL of normal saline over 20 min via another IV cubital line. Then, infusions of Cerebrolysin daily for 14 consecutive days.
The standard care is allowed for both groups.

Intervention Type
Drug

Phase
Phase III

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

Primary outcome measure
Current primary outcome measure as of 25/11/2024:
The rate of hemorrhagic transformation (both any and symptomatic) will be assessed using follow-up non-contrast brain computed tomography (CT) scans. CT scans will be performed 24 hours after IVT (visit 1), on day 7 (visit 2), day 14 (visit 3), and additionally if requested by the

treating neurologist.
Symptomatic intracranial hemorrhage will be defined according to the ECASS III criteria as any visible extravascular blood in the brain or cranium associated with clinical deterioration (an increase of ≥4 points on the NIH Stroke Scale [NIHSS]) or resulting in death.

Previous primary outcome measure:
Rate of hemorrhagic transformation (any and symptomatic) on any of follow-up non-contrast brain computed tomography (CT) scan. CT is performed 24 h after the IV TLT (visit 1), on day 7 (visit 2), 14 (visit 3) and if required by a treating neurologist. Symptomatic intracranial hemorrhage was defined according the ECASS III study as any apparently extravascular blood in the brain or within the cranium that is associated with clinical deterioration (an increase of ≥4 points on the NIHSS), or led to death.

Secondary outcome measures
Current secondary outcome measure as of 25/11/2024:
1. Functional outcome measured using the National Institutes of Health Stroke Scale (NIHSS) at 24 hours (visit 1), and on days 3 (visit 2) and 14 (visit 3)
2. Functional outcome measured using the modified Rankin Scale on day 90 (visit 4)
3. Permeability-surface area product measured using diffusion-tensor imaging (including fractional anisotropy, axial, radial, and mean diffusivity) and CT-perfusion imaging (measuring the) at 24 hours after intravenous thrombolysis (DTI only) and on day 14 (DTI and CTP)
4. Adverse events measured using interviews during follow-up at 24 hours, days 3, and 14, along with the evaluation of vital signs (blood pressure, heart rate), standard biochemical panel, and complete blood count at admission and on day 14

Previous secondary outcome measure:
1. Functional outcome measured using National Institutes of Health Stroke Scale (NIHSS) score at (visits 1, 2, 3 and on day 90 (visit 4)
2. Functional outcome measured using modified Rankin scale score at day 14 and 90
3. Blood-brain barrier permeability measures: fractional anisotropy, axial and radial diffusivity, permeability-surface area product measured using axial diffusion-tensor imaging at 24 h after the IV TLT, on day 14 and brain CT perfusion on day 14 and 90
4. Adverse events are assessed by interview during the follow-up
5. Vital signs (blood pressure, heart rate), standard biochemical panel and complete blood count (blood test) are evaluated at admission and on day 14
6. C-reactive protein is measured by blood test at visit 1

Overall study start date
24/04/2018

Overall study end date
30/11/2020

Eligibility

Participant inclusion criteria
Current participant inclusion criteria as of 25/11/2024:
1. Patients with a confirmed diagnosis of acute ischemic stroke (AIS)
2. Male or female participants

3. Age ≥18 years
4. Admission to one of the study sites within 4.5 hours of AIS onset
5. Indications for IVT

Previous participant inclusion criteria:
1. Patients with confirmed diagnosis of acute ischemic stroke (AIS)
2. Male or female gender
3. Age ≥18 years
4. Admission to one of the sites within 4.5 h after the AIS onset
5. Indications for intravenous thrombolytic therapy

Participant type(s)
Patient

Age group
Mixed

Lower age limit
18 Years

Sex
Both

Target number of participants
263

Total final enrolment
341

Participant exclusion criteria
Current participant exclusion criteria as of 25/11/2024:
1. Contraindications for IVT
2. Contraindications for Cerebrolysin
3. Evidence of hemorrhagic transformation or intracranial hemorrhage on the screening CT scan
4. Any other concurrent life-threatening medical conditions

Previous participant exclusion criteria:
1. Contraindications for intravenous thrombolytic therapy
2. Contraindications for Cerebrolysin
3. Signs of hemorrhagic transformation or intracranial hemorrhage on the screening CT scan
4. Any other concurrent life-threatening medical condition

Recruitment start date
29/04/2018

Recruitment end date
31/08/2020

Locations

Countries of recruitment
Russian Federation

Study participating centre
Interregional Clinical Diagnostic Center
12a Karbysheva str.
Kazan
Russian Federation
420101

Study participating centre
Municipal Clinical Hospital No. 7 of Kazan
54, M. Chuykova str.
Kazan
Russian Federation
420103

Study participating centre
Medical clinic of Kazan Federal University
1A, Chehova str.
Kazan
Russian Federation
420043

Study participating centre
Perm Territorial Clinical Hospital
85, Pushkina str.
Perm
Russian Federation
614045

Study participating centre
Emergency Medical Center of Naberezhnye Chelny
18, Naberezhnochelninskiy av.
Naberezhnye Chelny, Republic of Tatarstan
Russian Federation
423803

Study participating centre

Leninogorsk District Hospital
20, Sadrieva str.
Leninogorsk, Republic of Tatarstan
Russian Federation
423250

Study participating centre
Nizhnekamsk District Hospital
11, Ahtubinskaya str.
Nizhnekamsk, Republic of Tatarstan
Russian Federation
423577

Study participating centre
Arsk District Hospital
32, Komsomolskaya str.
Arsk, Republic of Tatarstan
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Sponsor information

Organisation
State Autonomous Institution of Health Interregional Clinical Diagnostic Center

Sponsor details
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Sponsor type
Hospital/treatment centre

Website
http://www.icdc.ru/en/

ROR
https://ror.org/059vcy092

Funder(s)

Funder type
Other

Funder Name
Investigator initiated and funded

Results and Publications

Publication and dissemination plan
Planned publication in an international peer-reviewed journal.

Intention to publish date
30/11/2021

Individual participant data (IPD) sharing plan
The anonymised dataset generated and analysed during the current study is available upon reasonable request from the corresponding author, Dr. Mikhail Kalinin, ninilak@gmail.com. The raw data of the post hoc analysis have been published as a supplement to the results publication.

IPD sharing plan summary
Available on request, Published as a supplement to the results publication

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Protocol file	Russian language	30/04/2018	01/03/2021	No	No
Protocol file	English language	30/04/2018	28/03/2023	No	No
Results article	results	27/03/2023	28/03/2023	Yes	No
Abstract results	Results abstract European Stroke Organisation Conference 2021	03/09/2021	29/03/2023	No	No
Results article		08/09/2023	11/09/2023	Yes	No
Other publications	Post hoc analysis	05/01/2024	22/01/2024	Yes	No
Abstract results		30/11/2023	23/01/2024	No	No
Other publications	Post hoc analysis	21/03/2024	02/04/2024	Yes	No
Preprint results		18/10/2024	21/10/2024	No	No
Abstract results	Post hoc analysis results: abstract EP025/#2725 - 16th World Stroke Congress	26/10/2024	25/10/2024	No	No

Statistical Analysis Plan	25/04/2024	20/11/2024	No	No
Other publications	22/03/2025	24/03/2025	Yes	No