ISRCTN70157009 https://doi.org/10.1186/ISRCTN70157009

Clot lysis: evaluating accelerated resolution of intraventricular haemorrhage Phase III

Submission date	Recruitment status	[_] Prospectively registered
16/12/2009	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
22/01/2010	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
04/08/2017	Circulatory System	

Plain English summary of protocol
Not provided at time of registration

Contact information

Type(s)
Scientific

Contact name
Ms Amanda Bistran-Hall

Contact details
Johns Hopkins Medical Institutions
Department of Neurology
Division of Brain Injury Outcomes
1550 Orleans Street
Suite 3M-50
Baltimore
United States of America
21231
+1 (0)410 955 2536
abistra1@jhmi.edu

Additional identifiers

ClinicalTrials.gov (NCT)
NCT00784134

Protocol serial number
IVH06

Study information

Scientific Title
A Phase III, randomised, placebo-controlled trial to evaluate the accelerated resolution of intraventricular haemorrhage by recombinant tissue Plasminogen Activator (rt-PA)

Acronym
CLEAR III

Study objectives
Aim:
To define precisely the long-term effects of lysing ventricular blood clots with rt-PA on the functional outcomes of cerebral haemorrhage patients. We propose to test if this intervention promotes a recovery of function, as defined as a modified Rankin Score of less than or equal to 3 at 180 days post ictus, by facilitating more rapid clot resolution as compared to treatment with extraventricular drainage (EVD) with placebo.

Primary hypothesis:
Clot removal with an EVD + rt-PA can increase the percent of patients with good functional outcomes, compared to management with EVD + placebo.

Secondary hypotheses:
1. Clot removal with EVD + rt-PA can increase the percent of patients with a good functional outcome, compared to management with EVD + placebo. For a disease with very high mortality, the 0-3 and 0-4 thresholds are the critical thresholds for evaluating a biologic benefit of intervention. Thus, these will be examined first. There is some degree of controversy in the literature regarding the choice of modified Rankin Scale (mRS) cut-off thresholds. Thus, the treatment effects for alternate definitions of 'good outcome' will also be estimated.
2. EVD + rt-PA for Intraventricular Haemorrhage (IVH) clot removal produces improved outcome (s) assessed by the ordinal mRS score when compared to EVD + placebo.
3. Mortality attributed to EVD + rt-PA treatment plus disease-associated adverse events are similar to the morbidity and mortality attributed to EVD + placebo in the first 30 days.
4. Mortality at 180 days post treatment for EVD + rt-PA treated patients will be improved as compared to that of patients managed with EVD + placebo.
5. Clot removal with EVD + rt-PA treatment produces improvements in functional outcome assessed by alternative outcome measures such as National Institute of Health Stroke Scale (NIHSS), Barthel Index, Glasgow Outcomes Scale, extended Glasgow Outcomes Scale and mRS.
6. EVD + rt-PA treatment of IVH leads to decreased intensity of hospital care compared to EVD + placebo. This includes fewer hospital days, Intensive Care Unit (ICU) days, decreased intensity of Intracranial Pressure (ICP) management, shorter periods of Cerebro-Spinal Fluid (CSF) drainage, lower utilisation of ventriculoperitoneal shunts, and fewer general critical care complications.
7. The amount of residual blood at 72 hours and removal rates are associated with functional outcome at 180 days post bleed.
8. Quality of Life (QOL). Clot removal with EVD + rt-PA leads to improved health related QOL as assessed by subject and surrogate QOL domains through the Stroke Impact Scale, EQ-5D, Preference-Based Stroke Index (PBSI), and time at home endpoints.

Ethics approval required
Old ethics approval format

Ethics approval(s)

Johns Hopkins Medicine Office of Human Subjects Research (JHM-IRB 5), 17/03/2009, ref: NA_00021659

Study design
International multicentre randomised double-blind placebo-controlled trial

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Intraventricular haemorrhage (IVH) or IVH with intracerebral haemorrhage (ICH)

Interventions
The intervention to be compared is EVD + rt-PA against EVD + placebo (normal saline). In the EVD + rt-PA group, a low dose (1.0 mg q 8 hours) of the thrombolytic rt-PA will be administered via an EVD to the intraventricular clot.

Intervention Type
Mixed

Primary outcome(s)
Recovery of function, as defined as a modified Rankin Score of ≤ 3, at 180 days post ictus

Key secondary outcome(s))
1. Percentage of patients with good functional outcomes using alternate definitions of "good outcome"
2. Functional outcomes, assessed by
2.1. Modified Rankin Scale (mRS)
2.2. National Institute of Health Stroke Scale (NIHSS)
2.3. Barthel Index
2.4. Glasgow Outcomes Scale
2.5. Extended Glasgow Outcomes Scale
3. Mortality at 30 and 180 days
4. Disease-associated adverse events at 30 days
5. Intensity of hospital care
5.1. No. of hospital days
5.1. No. of ICU days
5.3. Intensity of Intracranial Pressure (ICP) management
5.3. Duration of periods of Cerebro-Spinal Fluid (CSF) drainage
5.4. Incidence of ventriculoperitoneal shunt usage
5.5. Incidence of general critical care complications
6. Removal rates: Correlation between the amount of residual blood at 72 hours and functional outcome at 180 days post bleed
7. Quality of Life (QoL) assessed by subject and surrogate QoL domains through
7.1. Stroke Impact Scale
7.2. EQ-5D
7.3. Preference-Based Stroke Index (PBSI)
7.4. Time at home endpoints

Completion date
30/06/2015

Eligibility

Key inclusion criteria
1. Age 18-80.
2. Symptom onset < 24 hours prior to diagnostic CT scan.
3. Spontaneous Intracerebral haemorrhage (ICH) ≤ to 30cc and IVH obstructing 3rd and/or 4th ventricles.
4. ICH clot stability: ICH must be ≤ to 30cc on initial presentation and not exceed 35cc on subsequent pre-randomisation stability scans. A CT scan performed 6 hours or more after Intravenous catheter (IVC) placement must be stable (difference is less than or equal to 5 cc) compared to the most previous CT scan as determined by the (AxBxC)/2 method.
Temporary Criterion: If the clot is not stable (i.e., difference is greater than 5 cc), a repeat CT scan must be performed at least 6 hours later and compared to the most previous CT scan. Investigator may continue to screen every 2 hours up to 72 hours for the initial bleeding to stabilise, as long as the subject is able to receive drug administration within 72 hours of time of diagnostic CT scan and the clot remains less than or equal to 35 cc. If the size stabilises (i.e., enlargement less than or equal to 5 cc between 2 sequential CT scans) and remains less than or equal to 35 cc, the patient is eligible.
5. IVH clot stability: The width of the lateral ventricle most compromised by blood clot must not increase by more than 2 mm, allowing for movement of blood under influence of gravity.
Temporary Criterion: If the clot is not stable (i.e., difference is greater than 2 mm), a repeat CT scan must be performed at least 6 hours later and compared to the most previous CT scan. Investigator may continue to screen up to 72 hours for the initial bleeding to stabilise, as long as the subject is able to receive drug administration within 72 hours of time of diagnostic CT scan. If the size stabilises (i.e., enlargement less than or equal to 2 mm between 2 sequential CT scans), the patient is eligible.
6. Catheter tract bleeding must be less than or equal to 5cc on CT scan for stability.
Temporary Criterion: if a catheter tract haemorrhage is present on the CT scan done 6 hours after IVC placement and is greater than 5cc or greater than 5mm, obtain a repeat CT scan 12 hours later. If the catheter tract haemorrhage further enlarges by more than 5cc or more than 5mm as compared to the most previous CT scan, the investigator may continue to screen by repeat CT scan every 12 hours for the bleeding to stabilise, as long as the subject is able to receive drug administration within 72 hours of time of diagnostic CT scan. If the size stabilises (i.e., enlargement less than or equal to 5 cc or less than or equal to 5 mm between 2 sequential CT scans), the patient is eligible.
7. On stability CT scan, the 3rd and/or 4th ventricles are occluded with blood.
8. All patients randomised will have had EVD placed, ideally using no more than 2 complete passes (including "soft passes" using the original trajectory), on an emergent basis as defined by the "standard of care" neurosurgical/critical care decisions of the managing physicians. If more than 2 passes are required for placement, additional stabilisation of IVC site will be determined with a CT performed at 24 hours after IVC placement.
Temporary Criterion: If no IVC is in place at the time the patient is initially screened, the decision to place an IVC may occur after the patient is initially screened but an IVC must be in-place and stable at the time of randomisation.
9. Patients with primary IVH are eligible (i.e. with ICH=0).
10. Systolic Blood Pressure (SBP) < 200 mmHg sustained for the 6 hours before drug administration (closest to randomisation).

Temporary Criterion: Blood pressure inclusion criteria not met when patient is screened: most vital signs are stabilised within the time window for enrolment.
11. No test article may be administered until at least 12 hours after symptom onset.
12. Able to receive first dose within 72 hours of CT scan diagnosing IVH (provided the time of symptom onset to diagnostic CT does not exceed 24 hours).
13. Historical Rankin Score of 0 or 1.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
80 years

Sex
All

Key exclusion criteria
1. Suspected (unless ruled out by angiogram or Magnetic Resonance Angiography/Imaging [MRA /MRI]) or untreated ruptured cerebral aneurysm, ruptured intracranial arteriovenous malformation (AVM), or tumour. Treatment of an existing aneurysm or AVM must have occurred at least 3 months before the current onset.
Temporary Criterion: This is especially important in primary IVH, when no ICH source is found. A CT angiogram, angiogram or MRA/MRI is sufficient to continue the screening process: if negative, the patient is eligible.
2. Presence of choroid plexus vascular malformation or Moyamoya disease.
3. Clotting disorders.
Temporary Criterion: Reversing anticoagulation will be permitted where long term anticoagulation is not required. Subjects requiring long term anticoagulation are excluded.
4. Platelet count < 100,000, International Normalized Ratio (INR) > 1.3, or an elevated activated Partial Thromboplastin Time (aPTT).
Temporary Criterion: Low platelet counts etc. can normalise, on admission, within 24 hours, an INR can also normalise to less than or equal to 1.3.
5. Pregnancy (positive serum or urine pregnancy test).
6. Infratentorial haemorrhage (any involvement of the midbrain or lower brainstem as demonstrated by radiograph or complete third nerve palsy. Note: Patients with a posterior fossa ICH or cerebellar haematomas are ineligible.).
7. Subarachnoid Haemorrhage (SAH) at clinical presentation (an angiogram should be obtained when the diagnostic CT scan shows SAH or any haematoma location or appearance not strongly associated with hypertension. If the angiogram does not detect a bleeding source to account for the haemorrhage, the patient is eligible for the study.) Subsequent appearance of cortical SAH secondary to clot lysis is not a dosing endpoint.
Temporary Criterion: An angiogram can be obtained when the diagnostic CT scan demonstrates

subarachnoid haemorrhage or any haematoma location suggestive of aneurysm or spearing not strongly associated with hypertension. If the angiogram does not demonstrate a bleeding source that accounts for the haemorrhage, the patient is eligible for the study.
8. ICH/IVH enlargement that cannot be stabilised in the treatment time window.
Temporary Criterion: ICH enlargement during the 6 hour stabilisation period (6 hours after IVC placement): It is permitted to screen up to 72 hours after diagnostic scan. If the ICH clot stabilises (i.e., enlarges no more than 5cc) and does not exceed 35cc (an ICH clot size of 35cc allows for stabilisation of a 5cc expansion for those patients at the upper limit of the ICH clot size limit), the patient is eligible.
9. Ongoing internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts. (Patients with prior bleeding that is clinically stable for 12 hours or more without any coagulopathy or bleeding disorder are eligible).
10. Multi-focal, superficial bleeding observed at a multiple vascular puncture and access sites (e. g., venous cutdowns, arterial punctures) or site of recent surgical intervention.
11. Prior enrollment in the study.
12. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated.
Temporary Criterion: Although these situations are often irreversible, under other conditions, change can occur over 24 hours.
13. Planned or simultaneous participation (between screening and Day 30) in another interventional medical investigation or clinical trial. Patients involved in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
14. No subject or legal representative to give written informed consent.

Date of first enrolment
01/07/2009

Date of final enrolment
30/06/2015

Locations

Countries of recruitment
United Kingdom

Brazil

Canada

Germany

Israel

Spain

Switzerland

United States of America

Study participating centre

Johns Hopkins Medical Institutions
Baltimore
United States of America
21231

Sponsor information

Organisation
Individual Sponsor (USA)

Funder(s)

Funder type
Research organisation

Funder Name
National Institutes of Health (NIH) (USA)

Alternative Name(s)
US National Institutes of Health, Institutos Nacionales de la Salud, NIH, USNIH

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Funder Name
National Institute of Neurological Disorders and Stroke

Alternative Name(s)
National Institute of Neurological Disorders & Stroke, NIH/National Institute of Neurological Disorders and Stroke, NIH National Institute of Neurological Disorders and Stroke, The National Institute of Neurological Disorders and Stroke, National Institute of Neurological Disorders and Blindness, National Institute of Neurological and Communicative Disorders and Stroke, Instituto Nacional de Trastornos Neurológicos y Accidentes Cerebrovasculares, NINDS, NINDB, NINCDS

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	11/02/2017		Yes	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes