ISRCTN81927110 https://doi.org/10.1186/ISRCTN81927110

A phase III, randomized, open-label, 500-subject clinical trial of minimally invasive surgery plus rtPA in the treatment of intracerebral haemorrhage

Submission date
08/08/2014

Recruitment status
No longer recruiting

Registration date
08/08/2014

Overall study status
Completed

Last Edited
26/03/2019

Condition category
Surgery

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

Plain English summary of protocol

Background and study aims
This study will determine whether a drug named recombinant tissue plasminogen activator (rtPA) improves recovery in patients with blood clots in the brain when given by minimally invasive surgery, compared to standard medical management. This study is necessary because although rtPA has been approved for certain uses in humans, it is not yet approved for dissolving blood clots in the brain. The study premise is that removing the blood clot faster will reduce injury to the brain and improve the patient's long-term prognosis.

Who can participate?
This study is for people with intracerebral haemorrhage (bleeding in the brain).

What does the study involve?
Initial investigations will include a medical history, physical examination, blood and urine tests, tests of neurological condition, and CT scans. Patients will have a CTA or MRI scan to rule out other underlying conditions. Eligible patients or their consultee will be asked to sign a consent form and the patient will then be randomly assigned (like flipping a coin) to one of two groups. Patients in the rtPA group will have a small hole made in the skull, as much blood as can be easily removed will be taken out, and a catheter (tube) inserted into the blood clot. The drug will be given via the catheter three times a day for up to 3 days. Patients in the other group will have the standard medical care. All patients will be monitored closely for 6 days including daily CT scans of the head to check for any bleeding. Patients will return to clinic after 1, 6 and 12 months for neurological examinations with CT scans at 1 and 6 months. These visits will take about 2 hours and one assessment will be video recorded. At 3 and 9 months patients will receive telephone follow-ups that will take about 30 minutes.

What are the possible benefits and risks of participating?
Not provided at time of registration.

Where is the study run from?
This international study is coordinated from John Hopkins University (USA). In the UK the study sites are: Newcastle upon Tyne Hospitals NHS Foundation Trust, Southampton University Hospitals NHS Trust, Salford Royal NHS Foundation Trust, Imperial College Healthcare NHS Trust, King's College Hospital NHS Foundation Trust, Cambridge University Hospital NHS Foundation Trust.

When is the study starting and how long is it expected to run for?
From December 2013 to November 2018.

Who is funding the study?
National Institutes of Health (NIH) (USA).

Who is the main contact?
Dr Barbara Gregson
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Study website
http://braininjuryoutcomes.com/mistie-iii-about

Contact information

Type(s)
Scientific

Contact name
Dr Barbara Gregson

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Additional identifiers

EudraCT/CTIS number
2013-002818-12

IRAS number

ClinicalTrials.gov number
NCT01827046

Secondary identifying numbers
ICH02

Study information

Scientific Title
A phase III, randomized, open-label, 500-subject clinical trial of minimally invasive surgery plus rtPA in the treatment of intracerebral haemorrhage

Acronym
Minimally Invasive Surgery plus rT-PA for ICH Evacuation (MISTIE III)

Study objectives
Minimally invasive surgery (MIS) plus recombinant tissue plasminogen activator (rtPA) for three days improves functional outcome by a 12% increase in the modified Rankin Scale (mRS) score 0-3 compared to medically treated subjects at 180 days.

More details can be found here: http://public.ukcrn.org.uk/Search/StudyDetail.aspx?StudyID=17175

Ethics approval required
Old ethics approval format

Ethics approval(s)
USA: Office of Human Subjects Research Institutional Review Boards, Johns Hopkins Medicine, 21/11/2013, ref:NA00080619/CIR00004252
UK: Berkshire NRES Committee – South Central, 25/07/2014, ref: 14/SC/0228
Spain: Comité Ético De Investigatión Clínica, Hospital Universitario Río Hortega, Valladolid, 31/07/2014
Hungary: Regionális És Intézményi Humán Orvosbiológiai Kutatásetikai Bizottsága, University of Szeged, 04/11/2014, ref: 105/2014
All other centres will seek ethics approval before recruiting participants.

Study design
Randomised; Interventional; Design type: Treatment

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in a web format but can be obtained from the PI/Research Nurse at recruiting sites

Health condition(s) or problem(s) studied
Topic: Stroke; Subtopic: Acute Care; Disease: Drug type, Surgery used, In hospital study

Interventions
Suitable patients who fulfil all the inclusion criteria including consent will be randomised to receive either an operation to insert a catheter into the clot in the brain and receive up to nine doses of drug over a three-day period, or to receive medical treatment alone. Patients are followed up at 30, 90, 180, 270 and 365 days. At 30, 180 and 365 days they will be invited to clinic for a follow-up CT and assessments and at 90 and 270 days the assessments will be done by phone.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Recombinant tissue plasminogen activator

Primary outcome measure
Modified rankin; Timepoint(s): 180 days

Secondary outcome measures
Not provided at time of registration

Overall study start date
01/12/2013

Completion date
30/11/2018

Eligibility

Key inclusion criteria
1. Spontaneous supratentorial ICH = 30 mL diagnosed using radiographic imaging (CT, CTA, etc.), with a GCS = 14 or a NIHSS = 6. Six-hour clot size equal to the most previous clot size (within 5 mL) as determined by additional CT scans at least 6 hours apart using the ABC/2 method.
2. Symptoms less than 24 hours prior to diagnostic CT (dCT) scan (an unknown time of onset is exclusionary).
3. Intention to initiate surgery between 12 and 72 hours after dCT. First dose can be given within 76 hours after dCT (delays for post surgical stabilization of catheter bleeding or because of unanticipated surgical delay are acceptable with approved waiver from the CCC).
4. SBP < 180 mmHg sustained for six hours recorded closest to the time of randomization.
5. Historical Rankin score of 0 or 1.
6. Age = 18 and = 80.

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
Planned Sample Size: 500; UK Sample Size: 40

Key exclusion criteria
1. Infratentorial hemorrhage. Intraventricular hemorrhage requiring treatment with extraventricular drainage (obstruction of third and fourth ventricles). Thalamic bleeds with apparent midbrain extension with third nerve palsy or dilated and nonreactive pupils. Other (supranuclear) gaze abnormalities are not exclusions. Note: Patients with a posterior fossa ICH or cerebellar hematomas are ineligible. Irreversible impaired brain stem function (bilateral fixed, dilated pupils and extensor motor posturing), GCS = 4. Ruptured aneurysm, arteriovenous malformation (AVM), vascular anomaly, Moyamoya disease diagnosed with radiographic imaging. Patients with unstable mass or evolving intracranial compartment syndrome.
2. Platelet count < 100,000, INR > 1.4, or an elevated prothrombin time (PT) or activated partial thromboplastin time (aPTT). Any irreversible coagulopathy or known clotting disorder. Inability to sustain INR = 1.4 using short and long active procoagulants (such as but not limited to NovoSeven, FFP, and/or vitamin K). Subjects requiring long-term anticoagulation are excluded. Reversal of anticoagulation is permitted for medically stable patients who can realistically tolerate the short term risk of reversal. Patient must not require Coumadin (anticoagulation) during the first 30 days, and normalized coagulation parameters must be demonstrated, monitored closely and maintained during the period of brain instrumentation. Use of Dabigatran prior to symptom onset.
3. Internal bleeding, involving retroperitoneal sites, or the gastrointestinal, genitourinary, or respiratory tracts.
4. Superficial or surface bleeding, observed mainly at vascular puncture and access sites (e.g., venous cutdowns, arterial punctures, etc.) or site of recent surgical intervention.
5. Positive urine or serum pregnancy test in premenopausal female subjects without a documented history of surgical sterilization.
6. Allergy/sensitivity to rtPA. Prior enrollment in the study. Planned or simultaneous participation (between screening and Day30) in another interventional medical investigation or clinical trial. Patients in observational, natural history, and/or epidemiological studies not involving an intervention are eligible.
7. Subjects who are not expected to survive to the day 365 visit due to comorbidities and/or are DNR/DNI status prior to randomization are excluded. Any concurrent serious illness that would interfere with the safety assessments including hepatic, renal, gastroenterologic, respiratory, cardiovascular, endocrinologic, immunologic, and hematologic disease. Patients with a mechanical heart valve. Known risk for embolization, including history of left heart thrombus, mitral stenosis with atrial fibrillation, acute pericarditis, or subacute bacterial endocarditis. Any other condition that the investigator believes would pose a significant hazard to the subject if the investigational therapy were initiated.
8. Active drug or alcohol use or dependence that, in the opinion of the site investigator, would interfere with adherence to study requirements.
9. In the investigator's opinion, the patient is unstable and would benefit from a specific intervention rather than

supportive care plus or minus MIS+rtPA removal of the ICH.
10. Inability or unwillingness of subject or legal guardian/representative to give written informed consent.

Date of first enrolment
01/12/2013

Date of final enrolment
30/11/2018

Locations

Countries of recruitment
Australia

Canada

China

England

Germany

Hungary

Israel

Spain

United Kingdom

United States of America

Study participating centre
Wolfson Research Centre
Neurosurgical Trials Unit
3-4 Claremont Terrace
Newcastle upon Tyne
United Kingdom
NE2 4AE

Study participating centre
70+ other centres
United Kingdom
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Sponsor information

Organisation
Johns Hopkins University

Sponsor details
Baltimore
Baltimore
United States of America
21218

Sponsor type
University/education

ROR
https://ror.org/00za53h95

Funder(s)

Funder type
Government

Funder Name
National Institutes of Health (NIH); Grant Codes: 1U01NS080824-01A1

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United States of America

Results and Publications

Publication and dissemination plan
To be confirmed at a later date

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary

Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article	results	09/03/2019		Yes	No
Results article	results	01/06/2019		Yes	No
HRA research summary			28/06/2023	No	No