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ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy

Submission date	Recruitment status	[X] Prospectively registered
28/10/2011	No longer recruiting	[_] Protocol
Registration date	**Overall study status**	[X] Statistical analysis plan
04/11/2011	Completed	[X] Results
Last Edited	**Condition category**	[_] Individual participant data
29/05/2019	Circulatory System	

Plain English summary of protocol

Background and study aims
Ischaemic stroke is a common cause of death and disability. Recombinant tissue plasminogen activator (rtPA) (Actilyse) is the only approved treatment of acute ischaemic stroke. Early use (<4. 5 hours) is associated with improved outcomes in a broad spectrum of patients but has an increased risk of bleeding, the most serious of which is intracranial haemorrhage (ICH). Accumulating evidence indicates that a lower dose (0.6mg/kg) works at least as well as the current standard approved dose (0.9mg/kg) and may have a reduced risk of ICH. Similarly, there is increasing evidence that early intensive blood pressure control can improve outcome in ischaemic stroke and lower the risk of ICH after rtPA. The primary aims of this study are to compare effectiveness of low versus standard dose rtPA and to establish the effects of intensive versus current guideline recommended blood pressure (BP) lowering on death and disability in patients eligible for rtPA after acute ischaemic stroke. The secondary aims are to evaluate the treatments on ICH, disability, quality of life and health service use.

Who can participate?
Patients aged 18 or over with acute ischaemic stroke

What does the study involve?
1. Registration, baseline, and allocation to one of two treatments to be achieved in 30 minutes.
2. Patients will be followed daily for 1 week and at 28 and 90 days unless death occurs earlier. Follow-up data are collected at 24 and 72 hours, and 7 (or at time of death or hospital discharge if sooner), 28 and 90 days. The 90 day evaluation will be conducted in-person or by telephone by a trained local staff member who is blind to treatment allocation.
3. Brain imaging (CT scans or MRI) will be conducted according to standardised techniques at baseline, at 24±3 hours, and at a later stage in survivors who deteriorate or for other reasons.
The study has two treatment arms: arm [A] rtPA dose and arm [B] level of BP control. Patients will be allocated to Arm [A] rtPA-dose only, Arm [B] BP-lowering only or both [A] and [B,] depending of their eligibility.
1. Patients allocated into Arm [A] will be randomised by telephone call or via the web to a central office to receive standard-dose 0.9 mg/kg (maximum 90 mg) or low-dose 0.6 mg/kg (maximum 90 mg) i.v. rtPA (Actilyse).
2. Patients allocated into group [B] will be randomised into intensive BP lowering to a target

systolic BP range 140-150 mmHg within 30 minutes of commencing rtPA or guideline-based BP lowering to a target systolic BP of 185 mmHg prior to rtPA.

What are the possible benefits and risks of participating?
Treatment with lower-dose rtPA can potentially be as effective but safer (less incidence not only of ICH but also bleeding from others organs in the body) compared to the standard dose of rtPA, and early intensive BP lowering interventions have the potential to reduce to reduce the risk of intracranial haemorrhage in patients with acute ischaemic stroke treated with thrombolysis. In addition to the bleeding risk of standard-dose treatment with rtPA currently accepted in routine hospital practice, a potential risk associated with Part [A] of the study is that patients who are randomised to receive a low-dose of rtPA may have less dissolving of their clot and therefore a lower chance of subsequent brain recovery compared to those who receive a standard-dose of rtPA, but this is unknown. The potential risks associated with participating in Part [B] of the study are that patients receiving intensive blood pressure lowering treatment could potentially have more low blood pressure episodes with subsequent decreased blood flow in several organs, leading to damage to the kidneys or brain, but these risks are very low. This study aims to further medical knowledge and may in future improve treatment for patients with ischaemic stroke, however it may not directly benefit the patient.

Where is the study run from?
The study will be run by the George Institute of Global Health in Australia. Patients will be recruited from approximately 100 hospitals in Australia, Asia, Europe and South America.

When is the study starting and how long is it expected to run for?
The study will commence as a start-up phase during 2011, before moving to an expanded phase of recruitment during 2012-2016.

Who is funding the study?
Australian National Health Service and Medical Research Council

Who is the main contact?
Prof. Craig Anderson
canderson@george.org.au

Contact information

Type(s)
Scientific

Contact name
Prof Craig Anderson

Contact details
The George Institute for Global Health
Street: Level 10, King George V Building
Missenden Road, Royal Prince Alfred Hospital
Mail: PO Box M201, Missenden Road
Sydney
Australia
2217

Additional identifiers

EudraCT/CTIS number

IRAS number

ClinicalTrials.gov number
NCT01422616

Secondary identifying numbers
X11 - 0123 & HREC/11/RPAH/176, ACTRN12611000236998

Study information

Scientific Title
ENhanced Control of Hypertension ANd Thrombolysis strokE stuDy: a multicentre randomised trial

Acronym
ENCHANTED

Study objectives
In patients with acute ischaemic stroke eligible for thrombolysis with recombinant tissue plasminogen activator (rtPA) according to local guidelines and otherwise able to receive best usual medical care, the primary aims are to determine:
1. Whether compared to the standard dose, low-dose rtPA is at least as effective (not inferior) on death or any disability (i.e. null hypothesis is that low-dose is inferior to standard dose rtPA)
2. Whether compared with current guideline recommended criteria for blood pressure (BP) management, early intensive BP lowering is superior in reducing the risk of death or any disability (i.e. null hypothesis is that there is no difference in the intensities of BP control on this outcome).

The key secondary aims are to determine:
1. Whether compared with standard dose rtPA, low-dose rtPA reduces the risk of Symptomatic Intra-Cerebral Hemorrhage (sICH)
2. Whether compared with standard guideline-based BP management, early intensive BP lowering after rtPA reduces the risk of sICH (i.e. null hypothesis is that there is no difference in the rate of sICH between groups of differing intensities of BP lowering). Other secondary aims are to define the effects of the treatments on any ICH; a shift (improvement) in disability according to the modified Rankin Scale (mRS); separately on death and disability; early neurological deterioration; health-related quality of life (HRQoL); recurrent stroke and myocardial infarction; length of hospital stay; and need for permanent residential care.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Sydney South West Area Health Service Ethics Review Committee (RPAH Zone), 07/06/2011, ref: X11 - 0123 & HREC/11/RPAH/176

Study design
International multicentre prospective fixed-time point randomisation for two arms open blinded endpoint controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

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

Health condition(s) or problem(s) studied
Acute ischaemic stroke

Interventions
Randomised interventions: Randomisation is via a central internet-based system developed by The George Institute, Sydney, Australia, either direct or via a specially developed IVRS (only in China), stratified by country, site, time from onset (<3 vs ≥3 hours) and NIH Stroke Scale (NIHSS) (<10 vs ≥10) to ensure balance in key prognostic factors. Most patients will be eligible for arm [A] as the overall inclusion criteria is eligibility for rtPA, but only a proportion (~60%) of patients with acute ischaemic stroke are anticipated to have elevated blood pressure (BP) and thus eligible for arm [B]. Investigators have the choice of randomising patients into, one or both treatment arms: [A]: standard-dose 0.9 mg/kg (maximum of 90 mg) or low-dose 0.6 mg/kg (maximum of 90 mg) i.v. rtPA (Actilyse) and/or [B]: intensive BP lowering to a target systolic BP range 140-150 mmHg within 30 minutes of rtPA and to maintain this level for at least 72 hours (or until hospital discharge or death if this should occur earlier) or guideline-based BP lowering to a target systolic BP of <180 mmHg post-rtPA. Standardised locally approved i.v. BP lowering agents are to be used.

Intervention Type
Other

Phase
Not Applicable

Primary outcome measure
1. Compared with standard dose i.v. rtPA, low-dose rtPA is at least as effective (not inferior) on the major clinical outcome of death or any disability at 3 months (i.e. corresponding null hypothesis is that low-dose is inferior to standard dose rtPA);
2. Compared with standard guideline-based BP management, early intensive BP lowering is superior in reducing the risk of the major clinical outcome of death or any disability at 3 months (i.e. corresponding null hypothesis is that there is no difference in treatments on this outcome)

Secondary outcome measures
1. Compared with standard dose i.v. rtPA, low-dose rtPA reduces the risk of sICH
2. Compared with standard guideline-based BP management, early intensive BP lowering after thrombolysis with rtPA reduces the risk of sICH (i.e. corresponding null hypothesis is that there is no difference in the rate of sICH between groups of differing intensities of BP lowering).
3. To define effects on a shift (improvement) in measures of disability:
3.1. According to the grading system on the modified Rankin Scale (mRS)
3.2. Any ICH; separately on death and disability
3.3. Physical function
3.4. Early neurological deterioration
3.5. HRQoL
3.6. Major vascular events of recurrent stroke and myocardial infarction
3.7. Length of hospital stay
3.8. Need for permanent residential care and
3.9. Health care costs

Overall study start date
30/11/2011

Completion date
30/11/2016

Eligibility

Key inclusion criteria
1. General criteria for use of thrombolytic treatment with rtPA:
1.1. Adult (age ≥18 years)
1.2. A clinical diagnosis of acute ischaemic stroke confirmed by brain imaging
1.3. Able to receive treatment within 4.5 hours after the definite time of onset of symptoms
1.4. Have a systolic BP ≤185 mmHg (i.e. the guideline recommended level of eligibility for rtPA; patients with higher BP levels at presentation can still be included provided the BP is reduced to the entry level prior to commencement of the randomised treatment).
1.5. Provide informed consent (or via an appropriate proxy, according to local requirements)
2. Specific criteria for arm [A] of low-dose vs standard-dose rtPA.
2.1. No definite indication nor contraindication for either low-dose or standard-dose rtPA.
3. Specific criteria for arm [B] of intensive BP lowering vs guideline recommended BP control
3.1. Sustained elevated systolic BP level, defined as 2 readings ≥150 and ≤185 mmHg (i.e. the upper level for contraindication to use of thrombolysis)
3.2. No definite indication or contraindication to either immediate "intensive BP lowering (to a target of 140-150 mmHg systolic) versus guideline-based BP control (e.g. intensive BP lowering is feasible and does not appear to pose excessive hazard to the patient).

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
5000

Total final enrolment
4587

Key exclusion criteria
Patients will not be eligible if there is one or more of the following:
1. Unlikely to potentially benefit from the therapy (e.g. advanced dementia, known severe pre-stroke disability (mRS scores 3-5), or a very high likelihood of death within 24 hours of stroke onset
2. Other medical illness that interferes with outcome assessments and follow-uP

Date of first enrolment
30/11/2011

Date of final enrolment
30/11/2016

Locations

Countries of recruitment
Argentina

Australia

Austria

Belgium

Brazil

Chile

China

Colombia

France

Germany

Greece

Hong Kong

Italy

Korea, South

Norway

Portugal

Singapore

Spain

Sri Lanka

Sweden

Switzerland

Taiwan

Thailand

United Kingdom

Viet Nam

Study participating centre
The George Institute for Global Health
Sydney
Australia
2217

Sponsor information

Organisation
The George Institute for Global Health (Australia)

Sponsor details
c/o Sully Fuentes
Street: Level 10, King George V Building
Missenden Road, Royal Prince Alfred Hospital
Mail: PO Box M201, Missenden Road
Sydney
Australia
2217

Sponsor type
Research organisation

ROR
https://ror.org/023331s46

Funder(s)

Funder type
Government

Funder Name
Australian National Health Service and Medical Research Council (Australia)

Results and Publications

Publication and dissemination plan
Not provided at time of registration

Intention to publish date

Individual participant data (IPD) sharing plan

IPD sharing plan summary
Not provided at time of registration

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications	rationale, design, and progress	01/07/2015		Yes	No
Results article	alteplase-dose arm results	15/04/2018	29/05/2019	Yes	No
Results article	results	02/03/2019	29/05/2019	Yes	No
Statistical Analysis Plan	statistical analysis plan	01/07/2019		No	No