ISRCTN93732214 https://doi.org/10.1186/ISRCTN93732214

Tranexamic acid for IntraCerebral Haemorrhage (TICH-2)

Submission date 15/01/2013	**Recruitment status** No longer recruiting	✓ Prospectively registered ✓ Protocol added ✓ SAP added ✓ Results added ? Raw data not yet added ✓ Study completed
Registration date 17/01/2013	**Overall study status** Completed	
Last Edited 20/06/2023	**Condition category** Circulatory System	

Plain English Summary

Background and study aims
When someone has a stroke caused by bleeding into the brain (haemorrhagic stroke) permanent brain damage can occur and result in long-term disability. There is also a chance that the bleeding can increase, which may cause worse disability or be life threatening. This happens in approximately 20-30% of haemorrhagic stroke patients. At present there is no available treatment that is effective at reducing the bleeding in the brain and improving the recovery. In this trial, we want to test whether it is possible to give a drug (tranexamic acid) to people in the first few hours after a haemorrhagic stroke. We hope that we will be able to show that giving the drug may reduce the chances of dying and being left with disability after a haemorrhagic stroke. In this trial, the treatment we are testing is a drug, tranexamic acid, which encourages blood to clot to stop the bleeding. Continued or increased bleeding into the brain (haematoma expansion) is not uncommon in the first hours and days following a haemorrhagic stroke and increases the risk of the patient not recovering fully and being left with some disability. Stopping the bleeding in the first hours and days after stroke with medicine might help patients to recover better. Tranexamic acid is a tried and tested drug in other medical conditions that acts quickly to help the blood to clot and stop bleeding but is not given routinely after stroke. The aim of this study is to assess what effect tranexamic acid has on how people recover after a haemorrhagic stroke.

Who can participate?
Adults with an acute stroke caused by bleeding in the brain, within 8 hours of stroke onset. Participants will need to be able to complete all of the assessments, and will not have a diagnosis of another medical condition that is likely to interfere with the trial (e.g. terminal illness or pregnancy). Participants cannot be participating in other trials that are testing drugs.

What does the study involve?
Each participant's involvement in the study will last for 90 days. Participants will be randomly allocated to one of two treatments. Half of the participants will receive an injection of the drug tranexamic acid and the other half will have an injection of salt water as a dummy (placebo) treatment. The treatment (either tranexamic acid or dummy) will be given as an injection as soon as possible once participants have decided they wish to take part in the study. The treatment

will be given via a drip over about 8 hours. The treatment will be given once, and then the treatment will stop. During the next 7 days a nurse will check the participants condition, looking in particular for signs of side effects of the treatment. A brain scan will also be repeated the day after the treatment to assess the effects of the treatment. The researchers will contact their GP or check with the NHS Information Centre to check on their condition 3 months after the stroke and to confirm contact details. Participants will then be contacted for a telephone consultation with a member of the research team. It will involve asking how they feel life has been affected by the stroke and some brief memory tests.

What are the possible benefits and risks of participating?
Because tranexamic acid is already routinely used in a number of bleeding conditions, we expect the potential benefit of the drug (stopping bleeding into the brain) to outweigh the low risk of serious side effects (such as blood clots). However, we do not know this for certain and will monitor all participants closely for side effects. Treatment with any drugs can result in possible side effects, but the side effects from tranexamic acid are generally mild. They can include diarrhoea, low blood pressure and dizziness. The drug can also sometimes affect colour vision but this is rare. However, because the treatment works by stopping bleeding there is a chance it can cause an increase in blood clot formation. This can occur in the legs (deep vein thrombosis, DVT) or the lungs (pulmonary embolism, PE) and is potentially very serious and maybe even life-threatening. In a very large study in 20,000 people with serious bleeding, tranexamic acid was safe and reduced the number of people dying from bleeding. There was no increase in serious side effects, such as blood clots, in the patients who were treated with tranexamic acid.

Where is the study run from?
The study is being run from the University of Nottingham but is a multi centre trial, with centres in Denmark, Georgia, Hungary, Italy, Malaysia, Poland, Republic of Ireland, Spain, Sweden, Switzerland, Turkey and the UK.

When is the study starting and how long is it expected to run for?
March 2013 to May 2018

Who is funding the study?
The National Institute of Health Research (NIHR) (UK)

Who is the main contact?
Dr Nikola Sprigg
nikola.sprigg@nottingham.ac.uk

Study website
http://tich-2.org/

Contact information

Type(s)
Scientific

Contact name
Dr Nikola Sprigg

ORCID ID
http://orcid.org/0000-0002-5871-8168

Contact details
Stroke, Division of Clinical Neuroscience
Clinical Sciences Building
City Hospital
Hucknall Road
Nottingham
United Kingdom
NG5 1PB
-
nikola.sprigg@nottingham.ac.uk

Additional identifiers

EudraCT/CTIS number
2012-004108-37

IRAS number

ClinicalTrials.gov number
Nil known

Protocol/serial number
HTA 11/129/109; 13467

Study information

Scientific Title
Tranexamic acid for IntraCerebral Haemorrhage (TICH-2): a pragmatic phase III prospective double-blind randomised placebo-controlled trial

Acronym
TICH-2

Study hypothesis
When someone has a stroke caused by bleeding into the brain (haemorrhagic stroke) permanent brain damage can occur and result in long-term disability. There is also a chance that the bleeding can increase, which may cause worse disability or be life threatening. At present there is no effective treatment available to reduce the bleeding in the brain and improve the recovery. New treatments are being developed to treat stroke, but it can be very hard to test whether they work in the first few hours because often patients take longer than this to get to hospital and have investigations such as brain scanning. Also some treatments are not suitable for all patients.

In this trial, the aim is to test whether it is possible to give tranexamic acid to patients in the first few hours after a haemorrhagic stroke and find out if it reduces the chances of dying and being left with disability.

Tranexamic acid encourages blood to clot to stop the bleeding. Continued or increased bleeding into the brain (called haematoma expansion) is not uncommon in the first hours and days

following a haemorrhagic stroke and increases the risk of the patient not recovering fully and being left with some disability, or dying. Stopping the bleeding in the first hours after stroke with medications might help patients to recover better and reduce the number of patients who die.

The data will help doctors decide whether blood thickening treatments like tranexamic acid can be used in patients with acute haemorrhagic strokes to try and reduce death and disability and improve recovery.

Pilot study registered under ISRCTN50867461: http://www.isrctn.com/ISRCTN50867461

Added 12/10/2017:
Approval was obtained in 2015 for a nested sub-study to investigate the role of Magnetic Resonance Imaging (MRI) scans in the diagnosis and assessment of patients with intracerebral haemorrhage. The objective of the MRI substudy is to determine the effects of tranexamic acid on the perihaematoma oedema, the presence of remote diffusion weighted imaging hyperintense lesions (DWIHL), and extent of end-stage tissue injury surrounding the haematoma cavity. The tertiary end points are:
1. Prevalence of remote DWIHL on Day 5 MRI scan
2. Perihaematoma oedema volume and perihaematoma diffusion restriction on Day 5 MRI scan
3. Combined volume of the residual haematoma cavity and surrounding gliosis on the Day 90 MRI scan
Planned recruitment was a subset of 280 patients recruited to the main TICH-2 study. The first patient was recruited in July 2015, recruitment closed 30/09/2017. The sub-study was funded by the British Heart Foundation (grant number PG/14/96/31262). The sub-study will close on 31/05/2018.

More details can be found at: http://www.nets.nihr.ac.uk/projects/hta/11129109
Protocol can be found at: http://www.nets.nihr.ac.uk/__data/assets/pdf_file/0008/81197/PRO-11-129-109.pdf

Ethics approval required
Old ethics approval format

Ethics approval(s)
NRES Committee East Midlands - Nottingham 2, 23/11/2012, ref: 12/EM/0369

Study design
Pragmatic phase III prospective double-blind randomised placebo-controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Copies of patient information sheets, consent forms and other trial related documents can be found at: http://tich-2.org/ShWrtq5IdxUu8LdpTzMfD2U3Uh4.php

Condition
Stroke

Interventions
Intravenous tranexamic acid: 1g loading dose given as 100 ml infusion over 10 minutes, followed by another 1g in 250 ml infused over 8 hours. Comparator matching placebo (normal saline 0.9%) administered by identical regimen.

Intervention Type
Drug

Phase
Phase III

Drug/device/biological/vaccine name(s)
Tranexamic acid

Primary outcome measure
To assess whether tranexamic acid is safe and reduces death or dependency after primary intracerebral haemorrhage (PICH)
Death or dependency (ordinal shift on mRS) at day 90 will be analysed by intention-to-treat using ordinal logistic regression (OLR), with adjustment for minimisation factors. The assumption of proportional odds will be tested using the likelihood ratio test. Comparison of tranexamic acid versus control.

Secondary outcome measures
1. At day 7 (or discharge if sooner), neurological impairment (NIHSS)
2. At day 90, disability (Barthel index), Quality of Life (EuroQoL), cognition, cognition and mood (TICS and ZDS)
3. Safety: death, serious adverse events, thromboembolic events, seizures
4. Costs: length of stay in hospital, re-admission, institutionalisation
5. Radiological efficacy/safety (CT scan): change in haematoma volume from baseline to 24 hours, haematoma location, and new infarction

Overall study start date
01/03/2013

Overall study end date
31/05/2018

Eligibility

Participant inclusion criteria
Adult (≥18 years, either sex) patients with acute primary intracerebral haemorrhage (PICH) within 8 hours of stroke onset (where stroke onset time is unknown, the time of when last known well will be used)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
2000

Total final enrolment
2325

Participant exclusion criteria
1. Patients with intracerebral haemorrhage secondary to anticoagulation, thrombolysis or known underlying structural abnormality such as arterial venous malformation, aneurysm, tumour, venous thrombosis as cause for the intracerebral haemorrhage. Note it is not necessary to exclude an underlying abnormality prior to enrolment, but where a secondary cause of haemorrhage is known, these patients should not be recruited.
2. Patients for whom tranexamic acid is thought to be contraindicated
3. Patients with premorbid dependency (mRS>4)
4. Participation in another drug trial concurrently
5. Prestroke life expectancy <3 months (e.g. advanced metastatic cancer)
6. Coma Glasgow coma scale <5

Recruitment start date
01/03/2013

Recruitment end date
30/09/2017

Locations

Countries of recruitment
Denmark

England

Georgia

Hungary

Ireland

Italy

Malaysia

Poland

Spain

Sweden

Switzerland

Turkey

United Kingdom

Study participating centre
City Hospital
Nottingham
United Kingdom
NG5 1PB

Study participating centre
124 UK and international centres from 12 countries
United Kingdom
-

Sponsor information

Organisation
University of Nottingham (UK)

Sponsor details
Research & Innovation
Jubilee Conference Centre
Triumph Road
Nottingham
England
United Kingdom
NG8 1DH
-
BB-sponsor@exmail.nottingham.ac.uk

Sponsor type
University/education

Website
http://www.nottingham.ac.uk/

ROR
https://ror.org/01ee9ar58

Funder(s)

Funder type
Government

Funder Name
Health Technology Assessment Programme, grant ref: 11/129/109

Alternative Name(s)
NIHR Health Technology Assessment Programme, HTA

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
1. The study protocol for the main study is available at: http://tich-2.org /ShWrtq5IdxUu8LdpTzMfD2U3Uh4.php
2. The statistical analysis plan and the protocol for the MRI sub-study have both been submitted for publication
3. A publication will be drafted in mid-March 2018 following the primary data analysis
4. Dissemination of the results will be via an oral presentation at the European stroke conference and publication in either NEJM or Lancet is planned for May 2018

Intention to publish date
01/05/2018

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made 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?
Protocol article	protocol	01/08/2016		Yes	No
Statistical Analysis Plan	statistical analysis plan	20/12/2017		No	No
Protocol article	sub-study protocol	03/02/2018		Yes	No
Results article	results	26/05/2018		Yes	No
Statistical Analysis Plan	sub-study statistical analysis plan	13/06/2018		No	No
Results article	results	01/07/2019	22/07/2019	Yes	No
Results article	CT results in	01/01/2020	19/11/2019	Yes	No
Results article	results	01/04/2021	11/09/2020	Yes	No
Results article	results	01/02/2021	16/02/2021	Yes	No
Results article		01/08/2021	19/05/2021	Yes	No
Results article	Substudy results	21/03/2022	22/03/2022	Yes	No
Results article	Secondary analysis	12/06/2023	20/06/2023	Yes	No
HRA research summary			28/06/2023	No	No