

Efficacy of nitric oxide in stroke

Submission date 12/11/2002	Recruitment status No longer recruiting	<input checked="" type="checkbox"/> Prospectively registered <input checked="" type="checkbox"/> Protocol
Registration date 12/11/2002	Overall study status Completed	<input checked="" type="checkbox"/> Statistical analysis plan <input checked="" type="checkbox"/> Results
Last Edited 31/07/2017	Condition category Circulatory System	<input type="checkbox"/> Individual participant data

Plain English summary of protocol

Background and study aims

Lowering blood pressure reduces the risk of further strokes in patients who have already had one or more strokes. High blood pressure is common in the first hours and days following a stroke and increases the risk of the patient not recovering fully and being left with some disability. Lowering blood pressure in the first hours and days after stroke with medications might help patients to recover. Although at present we routinely treat high blood pressure long term after a stroke, we do not do so immediately after the stroke. We aim to find out what effect glyceryl trinitrate (or GTN) has on how well people recover from strokes. GTN is a tried and tested drug used in other medical conditions that acts quickly to relax blood vessels and lower blood pressure. The data will help doctors decide whether blood pressure lowering treatments like GTN can be used in patients with acute stroke to improve recovery. We also aim to assess whether or not usual blood pressure medicines should be stopped or continued for 7 days after a stroke.

Who can participate?

Adult (age > 18 years) patients presenting with an acute stroke syndrome with residual motor weakness within 48 hours of onset

What does the study involve?

Patients are randomly allocated to receive either transdermal glyceryl trinitrate patches (GTN) or no GTN for 7 days. Patients who are already receiving blood pressure lowering treatments are also randomly allocated to either continue or stop this treatment for 7 days.

What are the possible benefits and risks of participating?

Participation in the study may reduce the symptoms of the stroke or improve long-term recovery. The information received from patients involvement may benefit other people who may have a stroke in the future. All drugs have the possibility of side effects. The side effects from GTN are generally mild. They can include headache, low blood pressure and dizziness.

Where is the study run from?

The University of Nottingham (UK)

When is the study starting and how long is it expected to run for?

January 2004 to October 2013

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Prof. Philip Bath
enos@nottingham.ac.uk

Study website
<http://www.enos.ac.uk/>

Contact information

Type(s)
Scientific

Contact name
Prof Philip Bath

Contact details
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Additional identifiers

EudraCT/CTIS number
2004-003870-27

IRAS number

ClinicalTrials.gov number
NCT00989716

Secondary identifying numbers
N/A

Study information

Scientific Title
A prospective, collaborative, international, multicentre, randomised, parallel-group, single and outcome blinded, controlled, factorial trial to investigate the safety and efficacy of treatment with transdermal glyceryl trinitrate, a nitric oxide donor, and of continuing or stopping temporarily pre-stroke antihypertensive therapy, in patients with acute stroke

Acronym

ENOS

Study objectives

Three-quarters of patients are hypertensive at the presentation of acute stroke while a high blood pressure is independently associated with a poor outcome. No large trials have specifically assessed whether blood pressure should be actively altered during the acute phase of stroke although outcome was worse in some trials of calcium channel blockers and beta receptor antagonists, probably through negative effects on cerebral blood perfusion and cardiac output. However, small studies involving drugs from other antihypertensive classes, including nitric oxide donors, suggest they may reduce blood pressure without reducing cerebral blood flow. Similarly, no studies have assessed whether prior anti-hypertensive medication should be stopped or continued. A definitive trial is now required to:

1. Assess the balance of risk and benefit of lowering blood pressure immediately after ischaemic and haemorrhagic stroke.
2. Assess whether prior antihypertensive therapy should be continued or stopped temporarily after stroke.

Protocol can be found at: <http://www.enos.ac.uk/enosprotocolv15.pdf>

Further reading (added 28/01/2010):

1. The NeuroGrid stroke exemplar clinical trial protocol.
Wardlaw JM et al. International Journal of Stroke 2007;2:63-69
<http://www.ncbi.nlm.nih.gov/pubmed/18705995>
2. Effect of nitric oxide donors on blood pressure and pulse pressure in acute and subacute stroke.
Gray LJ et al. International Journal of Stroke 2007;2:63-69
<http://www.ncbi.nlm.nih.gov/pubmed/17904083>
3. Management of blood pressure in acute stroke.
Phillips at al. Canadian J Neurological Sciences 2002;29:404
<http://www.ncbi.nlm.nih.gov/pubmed/12463498>
4. ENOS Efficacy of Nitric Oxide in Stroke Trial.
Stroke Center Stroke Trials Registry (2002)
<http://www.strokecenter.org/trials/TrialDetail.aspx?tid=103>

Ethics approval required

Old ethics approval format

Ethics approval(s)

Trent Regional Ethics Committee (REC) and the National Research Ethics Service (NRES), 03/09/2001, ref: MREC/01/4/046

Study design

Prospective international multicentre randomised parallel-group double-blind placebo-controlled trial

Primary study design

Interventional

Secondary study design

Randomised controlled trial

Study setting(s)

Hospital

Study type(s)

Treatment

Participant information sheet

Patient information can be found at: <http://www.enos.ac.uk/enospisv211.pdf>

Health condition(s) or problem(s) studied

Acute stroke

Interventions

1. Glyceryl trinitrate (transdermal)
2. Continue/temporarily stop prior anti-hypertensive therapy

Intervention Type

Drug

Phase

Not Applicable

Drug/device/biological/vaccine name(s)

Glyceryl trinitrate

Primary outcome measure

Death and dependency (Rankin score more than two).

Secondary outcome measures

1. Events by 7 days - recurrent stroke, symptomatic deep vein thrombosis, symptomatic pulmonary embolism, blood pressure daily between 1 and 7 days
2. Hospital events - length of stay in hospital, discharge disposition (death, institution or home)
3. Outcome at 90 days - Barthel Index (less than 60, including death), Barthel Index more than 95 /100 at three months (good outcome), quality of life (EuroQol), abbreviated mental test score
4. Safety measures - death at 7 and 90 days, symptomatic intracranial haemorrhage at 7 days, major extracranial haemorrhage at 10 days

Overall study start date

01/01/2004

Completion date

31/10/2013

Eligibility**Key inclusion criteria**

1. Patients with acute ischaemic or haemorrhagic stroke within 48 hours
2. Systolic blood pressure 140-220 mmHg

Participant type(s)

Patient

Age group

Adult

Sex

Both

Target number of participants

3500+

Key exclusion criteria

1. Unconscious (Glasgow Coma Scale less than eight)
2. Definite need for nitrate therapy: concurrent myocardial infarction, unstable angina, left ventricular failure
3. Dehydration
4. Contraindication to nitrate therapy: hypersensitivity to nitrates, hypovolaemia, hypertrophic obstructive cardiomyopathy, aortic stenosis, cardiac tamponade, constrictive pericarditis, mitral stenosis, marked anaemia, closed-angle glaucoma, sildenafil (Viagra) within previous 24 hours
5. Systolic blood pressure less than 140 mmHg or more than 220 mmHg
6. Patients expected to require surgical intervention (e.g. clot evacuation, carotid endarterectomy) during the treatment or follow-up period
7. Refusal to consent
8. Patient dependent on others prior to stroke (e.g. Rankin score more than three)
9. Known intracerebral pathology other than ischaemic stroke, e.g. subarachnoid haemorrhage, brain tumour, cerebral abscess
10. Other serious condition which is likely to prevent outcome assessment, e.g. advanced cancer
11. Involvement in a trial of another experimental intervention (drug or surgery) for acute stroke
12. Not available for follow-up, e.g. no fixed address, overseas visitor
13. Females of childbearing potential, pregnancy or breastfeeding

Date of first enrolment

01/01/2004

Date of final enrolment

31/10/2013

Locations

Countries of recruitment

Australia

Canada

China

Denmark

Egypt

England

Georgia

Greece

Hong Kong

India

Ireland

Italy

Malaysia

New Zealand

Norway

Philippines

Poland

Romania

Singapore

Spain

Sri Lanka

Sweden

Türkiye

United Kingdom

Study participating centre

University of Nottingham

Nottingham

United Kingdom

NG5 1PB

Sponsor information

Organisation

University of Nottingham (UK)

Sponsor details

University Park
Nottingham
England
United Kingdom
NG7 2RD

Sponsor type

University/education

Website

<http://www.nottingham.ac.uk/SCS/Divisions/Stroke/index.aspx>

ROR

<https://ror.org/01ee9ar58>

Funder(s)**Funder type**

Charity

Funder Name

Medical Research Council: from 01/112006

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Funder Name

Singapore A*STAR (MRI sub-study)

Funder Name

Bupa Foundation: 01/042004 - 31/10/2006

Alternative Name(s)

Funding Body Type

Private sector organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location

United Kingdom

Funder Name

Medical Research Council (as part of NeuroGRID)

Alternative Name(s)

Medical Research Council (United Kingdom), UK Medical Research Council, MRC

Funding Body Type

Government organisation

Funding Body Subtype

National government

Location

United Kingdom

Funder Name

Hypertension Trust: 01/09/2002 - 31/08/2004

Alternative Name(s)**Funding Body Type**

Private sector organisation

Funding Body Subtype

Other non-profit organizations

Location

United Kingdom

Funder Name

UK Reichstadt bequest

Funder Name

Stroke Association

Alternative Name(s)**Funding Body Type**

Private sector organisation

Funding Body Subtype

Associations and societies (private and public)

Location

United Kingdom

Funder Name

University of Nottingham

Alternative Name(s)**Funding Body Type**

Private sector organisation

Funding Body Subtype

Universities (academic only)

Location

United Kingdom

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?
Abstract results		01/01/2005		No	No
Protocol article	protocol	01/11/2006		Yes	No
	interim results				

Interim results article		01/02/2009	Yes	No
Results article	results	01/03/2013	Yes	No
Results article	results	01/12/2013	Yes	No
Statistical Analysis Plan	statistical analysis plan	01/04/2014	No	No
Other publications	patient baseline characteristics	01/08/2014	Yes	No
Results article	results	14/02/2015	Yes	No
Results article	results	01/11/2015	Yes	No
Results article	results	01/01/2016	Yes	No
Results article	results	01/12/2017	Yes	No