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Efficacy of nitric oxide in stroke

Submission date 12/11/2002	**Recruitment status** No longer recruiting	[X] Prospectively registered [X] Protocol [X] Statistical analysis plan [X] Results [_] Individual participant data
Registration date 12/11/2002	**Overall study status** Completed	
Last Edited 31/07/2017	**Condition category** Circulatory System	

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
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Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
2004-003870-27

ClinicalTrials.gov (NCT)
NCT00989716

Protocol serial number
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

Study type(s)
Treatment

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(s)
Death and dependency (Rankin score more than two).

Key secondary outcome(s))
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

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

Healthy volunteers allowed
No

Age group
Adult

Sex
All

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
United Kingdom

England

Australia

Canada

China

Denmark

Egypt

Georgia

Greece

Hong Kong

India

Ireland

Italy

Malaysia

New Zealand

Norway

Philippines

Poland

Romania

Singapore

Spain

Sri Lanka

Sweden

Türkiye

Study participating centre
University of Nottingham
Nottingham
United Kingdom
NG5 1PB

Sponsor information

Organisation
University of Nottingham (UK)

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, Medical Research Committee and Advisory 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, Medical Research Committee and Advisory 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)
TheStrokeAssociation, TheStrokeAssoc

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)
The University of Nottingham

Funding Body Type
Private sector organisation

Funding Body Subtype
Universities (academic only)

Location
United Kingdom

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	01/03/2013		Yes	No
Results article	results	01/12/2013		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
Protocol article	protocol	01/11/2006		Yes	No
Abstract results		01/01/2005		No	No
Interim results article	interim results	01/02/2009		Yes	No
Other publications	patient baseline characteristics	01/08/2014		Yes	No
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Statistical Analysis Plan	statistical analysis plan	01/04/2014		No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes