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Efficacy of Nitric Oxide in Stroke-2

Submission date 23/03/2021	**Recruitment status** No longer recruiting	✓ Prospectively registered ✓ Protocol added ? SAP not yet added – Results not yet expected – Raw data not yet expected ✓ Record updated in last year
Registration date 31/03/2021	**Overall study status** Ongoing	
Last Edited 18/06/2024	**Condition category** Circulatory System	

Plain English Summary

Background and study aims
When someone has a stroke there are a few hours after the symptoms begin where the brain cells are at risk of dying but may still be saved. It is possible to give treatments for stroke to help save these 'at-risk' brain cells during the few hours and therefore prevent further injury. New treatments are being developed to treat stroke more effectively, 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.
High blood pressure is common in the first hours and days following a stroke and increases the risk of patients 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 doctors routinely treat high blood pressure long term after a stroke, they do not do so immediately after the stroke.
The aim of this study is to test a treatment that lowers blood pressure when given immediately on arrival at hospital and soon after patients have had a stroke.
The treatment is called glyceryl trinitrate (commonly known as GTN) and it is a tried and tested drug in other medical conditions such as angina. It acts quickly to relax blood vessels and lowers blood pressure which is very important after stroke. GTN has also been tested in more than 4000 patients with recent stroke and was safe and lowered blood pressure. Of these, a few hundred patients received treatment between 3 and 5 hours after stroke and appeared to benefit from a better outcome. More patients in this narrow time window now need to be tested, rather than earlier than 3 hours or after 5 hours because lowering blood pressure with GTN appears not to be beneficial then.
The results of the trial will help doctors decide whether blood pressure lowering treatments like GTN should be given to patients soon after they have a stroke to give them a better chance of recovery.

Who can participate?
Patients aged 18 years or above arriving at hospital with symptoms that suggest they have had a stroke (either a clot or a bleed)

What does the study involve?
Once a potential participant has been confirmed to have had a stroke, the study will be explained to them by the research staff. If they agree to continue to take part, they will be asked

to sign a consent form. If the participant has some problems signing then either a relative can sign for them or the research team can record that they have said that they have would like to continue to take part. The participant will have had all the normal medical tests and treatments for stroke. The hospital staff will then put a patch on the participants back followed by a further patch the day after their stroke. If the participant leaves hospital before the second patch, they won't need any more patches.
The patches will have either contain blood pressure lowering medicine or won't have any medicine in them. The decision about what patches the participants get will be decided by chance (rather like tossing a coin) and neither the participant nor the doctor or nurse are able to choose. This is called randomisation and is done by a special computer programme. This is important as it makes sure equal numbers of patients receive each treatment. This means it is a fair test between treatments. The patch is covered in gauze to try to make sure that the participant or their relatives and friends and the medical staff do not know what treatment they have had. This makes the design of the trial better. If they continue to take part in the study, they will still receive all the care that they would normally receive after a stroke.
At 3 and 12 months after the stroke, a researcher will telephone the participant. They will ask a number of questions to see how well they have recovered from the stroke.

What are the possible benefits and risks of participating?
Participation may reduce the symptoms of the stroke or improve long-term recovery. However, this cannot be promised. The information obtained from the study may benefit other people who have a stroke in the future. All drugs have the possibility of side effects. The side effects from the blood pressure lowering patch are generally mild. The research team will check if the participant has experienced any side effects from the patch. If so the patch can be removed.

Where is the study run from?
University of Nottingham (UK)

When is the study starting and how long is it expected to run for?
April 2020 to September 2024

Who is funding the study?
Nottingham Hospital's Charity Research Fund (UK)

Who is the main contact?
Diane Havard
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Study website
https://stroke.nottingham.ac.uk/enos-2/

Contact information

Type(s)
Public

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Scientific

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Additional identifiers

EudraCT/CTIS number
2020-001304-42

IRAS number
281728

ClinicalTrials.gov number
Nil known

Protocol/serial number
CPMS 45528, IRAS 281728

Study information

Scientific Title
Efficacy of Nitric Oxide in Stroke-2

Acronym
ENOS-2

Study hypothesis
To assess the feasibility of recruitment and safety of transdermal glyceryl trinitrate (GTN) versus sham applied between 3 and 5 hours of stroke to inform a definitive trial.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 30/06/2020, North West - Greater Manchester South Research Ethics Committee (3rd Floor, Barlow House, 4 Minshull Street, Manchester, M1 3DZ, UK; +44 (0)207 104 8010; gmsouth.rec@hra.nhs.uk), REC ref: 20/NW/0246

Study design
Prospective randomized single-blinded masked-endpoint phase IIb trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
See study outputs table

Condition
Stroke

Interventions
Current intervention as of 19/05/2022:
Patients will be randomized (1:1) to receive either glyceryl trinitrate patches or sham patches. Randomization will be performed by the Nottingham Stroke Trials Unit (STU) and involve computerised stratification by stroke type (IS or not known; ICH) and minimisation on age, severity, time, systolic blood pressure and candidate for or received reperfusion therapy. Patients, relatives, researchers and outcome assessors will be masked to treatment allocation

Active: Transdermal glyceryl trinitrate (GTN) 5 mg placed on back or shoulders and applied for 2 days.
Comparator: Transdermal Duoderm hydrocolloid dressing placed on back or shoulders and applied for 2 days.

Following 2 days of treatment both arms will have the same follow up - follow-ups will be carried out on Day 2, the day of death or discharge from hospital, and Day 90.

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Following 2 days of treatment both arms will have the same follow up - follow-ups will be carried out on Day 2, the day of death or discharge from hospital, day 90 and day 365.

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Glyceryl trinitrate

Primary outcome measure
Current primary outcome measures as of 26/05/2022:
1. Feasibility of recruitment assessed using recruitment data recorded throughout the 31 months of recruitment
2. Safety assessed using safety monitoring throughout the study

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Previous primary outcome measure:
The feasibility of recruiting 120 (100 ischaemic stroke/20 intra-cerebral haemorrhage) eligible stroke patients who consent to participate in the study within 12 months of the start date

Secondary outcome measures
Current secondary outcome measures as of 26/05/2022:
1. Blood pressure measured using standard sphygmomanometer at baseline, Day 0 post treatment, Day 1 during treatment
2. Disability measured using the National Institutes of Health Stroke Scale (NIHSS) at baseline and Day 2
3. Feeding and dysphagia measured using the Dysphagia Severity Rating Scale (DSRS) at Day 2
4. Hospital utilisation (thrombectomy, hemicraniectomy surgery, hyperacute stroke unit, rehabilitation, physiotherapy, occupational therapy, speech and language therapy, ITU use)

measured by review of medical notes at death/discharge
5. Functional ability measured using the modified Rankin scale (mRS) and Barthel index (BI) at Day 90
6. Cognition measured using the mini mental state examination (MMSE) at Day 90
7. Mood measured using the Zung Depression Scale (ZDS) at Day 90
8. Quality of life measured using EuroQoL (EQ5D) at Day 90

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3. Feeding and dysphagia measured using the Dysphagia Severity Rating Scale (DSRS) at Day 2
4. Hospital utilisation (thrombectomy, hemicraniectomy surgery, hyperacute stroke unit, rehabilitation, physiotherapy, occupational therapy, speech and language therapy, ITU use) measured by review of medical notes at death/discharge
5. Functional ability measured using the modified Rankin scale (mRS) and Barthel index (BI) at Day 90 and Day 365
6. Cognition measured using the mini mental state examination (MMSE) at Day 90 and Day 365
7. Mood measured using the Zung Depression Scale (ZDS) at Day 90 and Day 365
8. Quality of life measured using EurolQuol (EQ5D) at Day 90 and Day 365

Overall study start date
01/04/2020

Overall study end date
30/09/2024

Eligibility

Participant inclusion criteria
Current inclusion criteria as of 19/05/2022:
1. Adults (aged ≥18 years)
2. Presentation compatible with hyperacute stroke syndrome
3. One or more of the following symptoms present at time of enrolment: Dysphasia, neglect (NIHSS 1-2), hemianopia (NIHSS 1-3), or limb weakness (NIHSS on affected arm and/or leg 1-4)
4. Treatment can be commenced between 3 and 5 h from onset of symptoms (for patients with wake-up stroke, treatment no more than 5 h after patient awakens)
5. Systolic BP ≥120 mmHg
6. If a CT/MR scan has already been performed, then it shows acute intracerebral haemorrhage or ischaemic stroke, or is normal. (If a CT scan has not been performed then it should be performed as soon as possible after treatment.)
7. For participants who lack capacity to consent for themselves and have no relative/friend available: Waiver of consent for treatment to ensure GTN given in 3- to 5-h time-window (and thrombolysis not delayed if ischaemic stroke)

Previous inclusion criteria:
1. 120 adults (≥18 years old) with presentation compatible with stroke)

2. Treatment 3-5 hours post ictus (or from when last seen free of stroke symptoms)
3. Limb weakness at time of enrolment (NIHSS on affected are and/or leg 1-4)
4. Systolic blood pressure (≥120 mmHg)
5. If a CT/MR scan has already been performed, then it shows acute intracerebral haemorrhage or ischaemic stroke, or is normal
6. Waiver of consent for treatment to ensure GTN given in 3-5 hour time-window (and thrombolysis not delayed if ischaemic stroke)

Participant type(s)
Patient

Age group
Adult

Lower age limit
18 Years

Sex
Both

Target number of participants
120

Participant exclusion criteria
Current exclusion criteria as of 19/05/2022 (following amendment approved 18/05/2022):
1. mRS ≥4
2. Hypotension or shock (systolic <120 mmHg)
3. BP Glucose (BM stix or equivalent) <3 mmol/l
4. Glasgow coma scale ≤8
5. Witnessed seizure at presentation
6. Known life expectancy <6 months
7. Patient presenting with sensory symptoms only
8. Known stroke mimic, aneurysmal subarachnoid haemorrhage, or haemorrhage due to venous thrombosis
9. Known allergy to glyceryl trinitrate (Transiderm-Nitro) patch
10. Known sensitivity to Duoderm hydrocolloid dressing
11. Planned for palliative care only
12. Recent use of phosphodiesterase type 5 (PDE5) inhibitors, e.g., sildenafil (Viagra®)
13. If a CT/MR scan has already been performed, then it shows a non-stroke lesion that explains the acute presentation
14. Known previous enrolment in ENOS-2

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Previous exclusion criteria as of 03/09/2021 (following amendment approved 25/08/2021):
1. mRS ≥4
2. Glucose (BM stix or equivalent) <3 mmol/l
3. Glasgow coma scale ≤8
4. Witnessed seizure at presentation
5. Known life expectancy <6 months
6. Known stroke mimic, aneurysmal subarachnoid haemorrhage, or haemorrhage due to venous thrombosis

7. Systolic blood pressure <120 mmHg
8. Known allergy to glyceryl trinitrate (Transiderm-Nitro) patch
9. Known sensitivity to Duoderm hydrocolloid dressing
10. Planned for palliative care only
11. Known previous enrolment in ENOS-2

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Previous exclusion criteria:
1. Patient from a nursing home
2. Glucose (BM stix or equivalent) <3 mmol/l
3. Glasgow coma scale ≤8
4. Witnessed seizure at presentation
5. Known life expectancy <6 months
6. Known stroke mimic, aneurysmal subarachnoid haemorrhage, or haemorrhage due to venous thrombosis
7. Systolic blood pressure <120 mmHg
8. Known allergy to glyceryl trinitrate (Transiderm-Nitro) patch
9. Known sensitivity to Duoderm hydrocolloid dressing
10. Planned for palliative care only
11. Known previous enrolment in ENOS-2

Recruitment start date
29/07/2021

Recruitment end date
29/06/2024

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Nottingham University Hospitals Trust
Queens Medical Centre
Derby Road
Nottingham
United Kingdom
NG7 2UH

Sponsor information

Organisation

University of Nottingham

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Sponsor type
University/education

Website
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ROR
https://ror.org/01ee9ar58

Funder(s)

Funder type
Charity

Funder Name
Nottingham Hospital's Charity Research Fund

Results and Publications

Publication and dissemination plan
Publication in a peer-reviewed high impact journal

Intention to publish date
31/05/2025

Individual participant data (IPD) sharing plan
The datasets generated and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary
Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version V1.2	01/07/2020	31/03/2021	No	Yes
Participant information sheet	version 1.2	14/05/2021	27/10/2021	No	Yes
Participant information sheet	version 1.3	12/04/2022	19/05/2022	No	Yes
Protocol file	version 3.0	14/09/2022	03/02/2023	No	No
HRA research summary			28/06/2023	No	No