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Mannitol for stopping or preventing brain swelling (cerebral oedema) after stroke from bleeding in the brain (intracerebral haemorrhage): a feasibility study

Submission date
05/10/2022

Recruitment status
No longer recruiting

Registration date
18/05/2023

Overall study status
Completed

Last Edited
17/02/2026

Condition category
Nervous System Diseases

[X] Prospectively registered

[X] Protocol

[_] Statistical analysis plan

[X] Results

[_] Individual participant data

Plain English summary of protocol

Background and study aims
Stroke from bleeding into the brain, known as intracerebral haemorrhage(ICH) affects about 15,000 adults in the UK each year and to-date there is no effective treatment. Brain swelling after ICH is common and can worsen damage resulting in disability or death. Large haemorrhages (~10-15%) cause brain swelling very quickly and the only option that is possible in some young patients is to do a major operation and make more space for the brain to expand. It is unclear whether surgery is beneficial and the operation has its own risks. So, finding treatments which prevent or stop brain swelling after ICH could reduce death or disability. Mannitol is a widely available drug and as an injection through a vein can reduce brain swelling after severe head injury or liver damage. It is cheap and easy to give. Small studies suggest that mannitol may also reduce brain swelling after ICH, but no definite study has been performed. We want to test if it is possible to do a small study of mannitol in ICH to find out how acceptable and manageable it is to inform a larger study.

Who can participate?
Forty-five adult patients with ICH with or at risk of brain swelling from ten UK hospitals will be recruited within 72 hours after stroke.

What does the study involve?
Using a computer, participants will be allocated like the roll of a dice to one of three groups: single mannitol injection; two mannitol injections or standard medical care alone.
Participants will be monitored for side effects, urine output, undergo blood tests and clinical assessments during and after treatment. We will do a repeat brain scan 5-7 days after treatment to see whether mannitol has reduced brain swelling. At 6 months, information on survival, participant's quality of life, mood, memory, disability and health problems in those who had Covid will be collected through telephone postal structured questionnaires. If a participant is unable to provide information, we will contact their relative/carer or GP.

What are the possible benefits and risks of participating?
Participation in this study may reduce the symptoms of intracerebral haemorrhage, reduce mortality, and may improve long-term recovery. We hope that the information we get will provide benefit to other people who have a stroke in the future.
Common side effects of mannitol are increased urination, nausea, vomiting, fever, chills, headache, runny nose, chest pain, rash, dizziness, or blurred vision. The drug can cause burning, pain or swelling around the needle when it is given as an injection and the treating team will closely monitor you for this.
Mannitol can affect the salt levels in the blood, cause damage to the kidneys, worsen bleeding in the brain, or lung congestion.
Because mannitol is already routinely used to reduce brain swelling from liver damage or severe head injury, we expect the potential benefits of the drug (stopping or preventing brain swelling in intracerebral haemorrhage) to outweigh the risk of side effects.

Where is the study run from?
Nottingham University Hospitals NHS Trust (UK)

When is the study starting and how long is it expected to run for?
October 2022 to November 2024

Who is funding the study?
NIHR Research for Patient Benefit Programme (UK)

Who is the main contact?
The email address for the CI requires updating to kailash.krishnan@nhs.net

Contact information

Type(s)
Principal investigator

Contact name
Dr Kailash Krishnan

Contact details
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH
+44 115 9249924
kailash.krishnan@nhs.net

Type(s)
Public

Contact name
Dr MACE-ICH trial team

Contact details

Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
United Kingdom
NG7 2UH
None available
mace-ich@nottingham.ac.uk

Additional identifiers

Clinical Trials Information System (CTIS)
2022-000283-22

Integrated Research Application System (IRAS)
1004870

Protocol serial number
22SR001

Study information

Scientific Title
MAnnitol for Cerebral oEdema after IntraCerebral Haemorrhage (MACE-ICH): a feasibility trial

Study objectives
Primary objective:
To assess the feasibility of screening, randomising, administering mannitol to acute intracerebral haemorrhage patients with cerebral oedema or at risk and completing follow-up to inform the design and conduct of an adequately powered, pragmatic, prospective, definitive trial.

Secondary objective:
To provide preliminary data on the effect of mannitol on secondary outcomes including clinical, radiological, laboratory, safety and health-economics.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 10/05/2023, East Midlands - Leicester Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA, UK; +44 207 104 8066; Leicestercentral.rec@hra.nhs.uk), ref: 22/EM/0242

Primary study design
Interventional

Study design
Interventional randomized parallel group controlled trial

Study type(s)

Treatment

Health condition(s) or problem(s) studied
Acute intracerebral haemorrhage (ICH)

Interventions
There are three arms in the MACE-ICH study, and patients are randomised into one of the arms via a 1:1:1 online, bespoke, randomisation system, built specifically for the purpose of the trial. The randomisation system will only be accessible for members of the research team who have been trained and delegated by their local Principal Investigator. The arms are as follows:
1. One dose of manntiol: Manntiol (1g/kg of 10% IV infusion at 10ml/min) + Standard care on Day 0; blood tests performed on day 1; CT head scan on day 5 (±2); day 28 follow-up by research team; day 180 follow-up by central trial office (MACE-ICH team based in Nottingham).
2. Two doses of mannitol: Manntiol (1g/kg of 10% IV infusion at 10ml/min) + Standard care on Day 0; blood tests performed on day 1; if blood tests, specifically serum osmolality, are stable then participants receive a second dose of mannitol (1g/kg of 10% IV infusion at 10ml/min); blood tests done again on day 2; day 28 follow-up by research team; day 180 follow-up by central trial office (MACE-ICH team based in Nottingham).
3. Standard care (e.g., at the clinician's discretion: IV fluids, nasogastric tube, other medications); blood tests performed on day 1; CT head scan on day 5 (±2); day 28 follow-up by research team; day 180 follow-up by central trial office (MACE-ICH team based in Nottingham).

Intervention Type
Drug

Phase
Phase II

Drug/device/biological/vaccine name(s)
Mannitol

Primary outcome(s)
1. Number of patients: screened and eligible: collected on screening logs that are requested from sites on a monthly basis.
2. Number of eligible patients recruited and reasons for not recruiting: collected on screening logs that are requested from sites on a monthly basis.
3. Proportion of eligible patients who received allocated treatment and reasons for non-allocation: This can be retrieved from the bespoke MACE-ICH database, whenever it is needed.
4. Recruitment rate derived from the sample size: This can be retrieved from the bespoke MACE-ICH database, and this data can also be collected on screening logs that are requested from sites on a monthly basis.
5. Treatment adherence: This can be continuously monitored, throughout the duration of the trial, within the bespoke MACE-ICH database.
6. Retention rate (number of participants with complete follow-up data at 180 days as a proportion of those randomised): This can be continuously monitored, throughout the duration of the trial, within the bespoke MACE-ICH database. All completed follow-ups will be visible in the MACE-ICH bespoke database.
7. Number of patients with outcome data and reasons for non-availability: This data will be continuously monitored within the MACE-ICH bespoke database. Any reasons for missing data will be collected by the monitor.
8. Effectiveness of blinded follow-up: Day-180 follow-up data will be checked by the trial

monitor.
9. Incidence and type of adverse events, protocol violations and trial withdrawal. This data will be continuously monitored within the MACE-ICH bespoke database, in conjunction with any adverse event/protocol violation logs that are available to monitor.

Key secondary outcome(s)

1. Laboratory tests (U&E's; e-GFR; serum osmolality): measured on days 1 and 2 (day 2 only for patients randomised to receive two doses of mannitol)
2. Participants' levels of consciousness are measured using the Glasgow Coma Scale (GCS) on day 5+/-2,
3. Participants' stroke severity is measured using the National Institutes Health Stroke Scale (NIHSS) on day 5+/-2,
4. Number of patients who had urinary tract infection collected from medical records on day 5±2 and day 28,
5. Number of patients who had sepsis collected from medical records on day 5±2 and day 28,
6. Mortality collected from medical records on day 5±2 and day 28
7. Participants' disability is measured using the Barthel Index on day 180,
8. Participants' mood is measured using the Zung depression scale [ZDS] on day 180,
9. Participants' cognition is measured using the TICS-M assessment on day 180,
10. Participants' quality of life is measured using the Euro-[EQ] QOL and EQ-VAS, on day 180,
11. Health economic assessment is measured using the EQ-5D questionnaire on day 180,
12. Participants' death or dependency is measured using the modified Rankin scale (mRS) on day 180,
13. Participants' length of stay in hospital is collected from the participant on the day-180 telephone questionnaire,
14. Participants' discharge destination is collected from the participant on the day-180 telephone questionnaire,
15. Long-term outcomes post Covid-19 and ICH is collected from the participant on the day-180 telephone questionnaire,
16. Number of patients who were transferred to high dependency unit - this can be continuously monitored, throughout the duration of the trial, within the bespoke MACE-ICH database.
17. Number of patients needing high dependency or intensive care unit - this can be continuously monitored, throughout the duration of the trial, within the bespoke MACE-ICH database.
18. Number of patients undergoing neurosurgical intervention - this can be continuously monitored, throughout the duration of the trial, within the bespoke MACE-ICH database.
19. Participants' recurrent strokes (if applicable) data will be collected throughout the trial by sites completing SAE reporting forms.
20. Number of patients intubated and ventilated - his can be continuously monitored, throughout the duration of the trial, within the bespoke MACE-ICH database.
21. The Follow-up CT scan on day 5±2 days will assess changes in oedema volume, oedema extension distance, haematoma volume, midline shift and hydrocephalus.

22. Safety Outcomes:
All safety outcomes (e.g. death; thrombophlebitis; hyper/hyponatremia; pulmonary oedema; hypotension; renal impairment and serious adverse events) will be continuously reported and recorded until day 180.

Completion date

30/11/2025

Eligibility

Key inclusion criteria
1. Adults (>18 years); spontaneous ICH confirmed by CT scan with estimated largest diameter > 2 cm;
2. </= 72 hour of ictus (or from last seen healthy);
3. Cerebral oedema with or without evidence of mass effect;
4. At risk of developing oedema (limited GCS <9 (eye opening and motor only) and NIHSS>/=8);
5. Signed consent (patient, personal or professional representative or independent physician)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
18 Years

Upper age limit
110 Years

Sex
All

Total final enrolment
46

Key exclusion criteria
1. GCS<5; premorbid mRS >3;
2. Isolated subarachnoid haemorrhage;
3. Haemorrhage known to be from: trauma or venous thrombosis or arteriovenous malformation or brain tumour or transformation of cerebral Infarct or cerebral aneurysm or thrombolytic drug;
4. Known hypersensitivity to mannitol;
5. Severe renal failure (e-GFR<30ml/min or dialysis);
6. Cardiac failure;
7. Hypotension at baseline (SBP <90 mm Hg);
8. Anuria;
9. Patient unwilling to participate;
10. Geographical or other factors which prohibit follow-up;
11. Pre-existing comorbidity with pre-ictal life expectancy <6 months;
12. Severe dementia;
13. Planned for palliative care;
14. Severe hypernatremia (sodium >160 mmol);
15. Severe hyponatremia (sodium <125 mmol);
16. Women of child-bearing age with a positive pregnancy test at the time of admission or lactating;

17. Patients in whom peripheral intravenous cannula cannot be placed;
18. Planned neurosurgery

Date of first enrolment
14/02/2024

Date of final enrolment
15/04/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
Queen's Medical Centre
Nottingham University Hospitals NHS Trust
Derby Road
Nottingham
England
NG7 2UH

Study participating centre
Royal Derby Hospital
University Hospitals of Derby and Burton NHS Foundation Trust
Uttoxeter Road
Derby
England
DE22 3NE

Study participating centre
Yeovil District Hospital
Yeovil District Hospital NHS Foundation Trust
Higher Kingston
Yeovil
England
BA21 4AT

Study participating centre
Addenbrooke's Hospital
Cambridge University Hospitals NHS Foundation Trust
Hills Road
Cambridge

England
CB2 0QQ

Study participating centre
Royal London Hospital
Whitechapel
London
England
E1 1BB

Study participating centre
Royal Devon and Exeter Hospital
Royal Devon and Exeter NHS Hospital Foundation Trust
Barrack Road
Exeter
England
EX2 5DW

Study participating centre
Royal Stoke University Hospital
Newcastle Road
Stoke-on-Trent
England
ST4 6QG

Study participating centre
Queen Elizabeth University Hospital
1345 Govan Road
Glasgow
Scotland
G51 4TF

Study participating centre
Aberdeen Royal Infirmary
Foresterhill Road
Aberdeen
Scotland
AB25 2ZN

Study participating centre
University Hospital of North Tees
Hardwick Road
Stockton-on-tees
England
TS19 8PE

Sponsor information

Organisation
Nottingham University Hospitals NHS Trust

ROR
https://ror.org/05y3qh794

Funder(s)

Funder type
Government

Funder Name
Research for Patient Benefit Programme

Alternative Name(s)
NIHR Research for Patient Benefit Programme, Research for Patient Benefit (RfPB), The NIHR Research for Patient Benefit (RfPB), RfPB

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a non-publically available repository. We use bespoke, secure, encrypted systems, that are only accessible by members/coordinators in the central research team. All individuals who have

access will be approved and delegated by local PI/CI. One system will store patients' data, including contact details, addresses and next-of-kin contact details (required for the day 180 follow-up). To access this system, users must be using the University of Nottingham network, or be connected to the University of Nottingham VPN. The other bespoke database will store all of the data collected for the day 0, day 1-2, day 5 +/-2, day 28 and day 180 assessments. There is currently no weblink for these sites as they are still in development, however we have used almost-identical systems for our other stroke clinical trials in Nottingham. Data will be available until the trial is complete; all data will be stored and archived after trial completion, in compliance with the University of Nottingham's archiving procedures.

Patients that fit the eligibility criteria will provide informed consent, however consent may also be sought from a legal representative if the patient lacks capacity to consent themselves. All un-anonymised consent forms will be uploaded to the secure bespoke system, and will only be accessible by a select few members of the central trial team in Nottingham (for monitoring purpose only). Any other documents uploaded for the purposes of monitoring will have all patient identifiers removed, in accordance with GCP. A unique ID number will be provided for each patient that is randomised into the trial.

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		12/02/2026	17/02/2026	Yes	No
Protocol article		28/07/2025	29/07/2025	Yes	No
HRA research summary			20/09/2023	No	No
Study website	Study website	11/11/2025	11/11/2025	No	Yes