EXTENDED SYNPOSIS

EuroHYP-1: A European, multicentre, randomised, phase III, clinical trial of hypothermia plus medical treatment versus best medical treatment alone for acute ischaemic stroke

BACKGROUND

Stroke is the second cause of death world-wide and the second cause of lost disability-adjusted life years in high-income countries. Because stroke incidence rises exponentially with age, the social and economic burden of stroke will rise further with the ageing of the population. The large majority of strokes (about 80%) are caused by arterial or arteriolar occlusion. Treatment options for these ischaemic strokes are extremely limited.

Systematic review of animal studies modelling ischaemic stroke suggests that cooling is the most promising intervention identified to date. In these animal studies, cooling to 35˚C reduced infarct size by about one third, and cooling to 34°C by around 45%. Moreover, several prospective observational studies in stroke have shown an association between raised body temperature and poor outcome, and between low body temperature and good outcome. Finally, cooling improves outcome in patients with hypoxic-ischaemic brain injury after cardiac arrest. Hypothermia is therefore the most promising treatment for patients with acute ischaemic stroke. Cooling awake patients with ischaemic stroke to 35°C has been shown feasible and safe, but whether this improves functional outcome has not yet been tested in an adequately-sized randomised clinical trial.

AIM

To determine whether systemic cooling to a target temperature of 34 to 35°C, started within 6 hours of symptom onset and maintained for 24 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke.

METHODS

This is an open, randomised, phase III, multicentre, international clinical trial with masked outcome assessment testing the benefits and harms of therapeutic cooling in 1500 awake adult patients with acute ischaemic stroke.

Inclusion criteria

1. A clinical diagnosis of acute ischaemic stroke;
2. A possibility to initiate cooling within 6 hours of symptom onset AND within 90 minutes of start of thrombolysis, OR within 90 minutes of hospital admission in patients who are not treated with thrombolysis;
3. A score on the national Institutes of Health Stroke Scale (NIHSS) of 6 up to and including 18 at the time of study inclusion;
4. Age ≥ 18 years;
5. Written informed consent.

Exclusion criteria

1. Evidence from a CT or MRI scan or from other pre-randomisation investigations of an intracranial haemorrhage, a tumour, encephalitis, or any diagnosis other than acute ischaemic stroke likely to be the cause of present symptoms. Haemorrhagic transformation of the infarct is not an exclusion criterion, except when there is a parenchymal haematoma covering more than 30% of the infarcted area, with significant space-occupying effect, or when there is a bleeding remote from the infarcted area (PH2 on Fiorelli's scale);

2. Conditions that may be exacerbated by hypothermia, such as haematological dyscrasias, oral anticoagulant treatment with INR ≥ 1.7, severe pulmonary disease, severe heart failure (defined as a New York Heart Association (NYHA) score of III or IV), history of myocardial infarction within the previous 3 months, angina pectoris in the previous 3 months, severe infection with a C-reactive protein > 50 mg/dl, or a clinical diagnosis of sepsis;
3. Blood oxygen saturation below 94%, allowing a maximum of 2 L/min oxygen delivered nasally to achieve this;
4. Bradycardia (<40 beats/min);
5. Body weight > 120 kg;
6. Pre-stroke score on the mRS > 2;
7. Allergy to pethidine, use of a monoamine oxidase inhibitor such as selegiline in the previous 14 days, severe hepatic dysfunction, or severe renal dysfunction;
8. Pregnancy. Women of childbearing potential are excluded unless a negative test for pregnancy has been obtained prior to randomisation;
9. Other serious illness that may confound treatment assessment or increase the risks of cooling;
10. Previous participation in this trial;
11. Social or other conditions that according to the investigator's judgement might be a major problem for follow-up.

Treatment

Cooling will be initiated within 6 hours of symptom onset with an intravenous infusion of 20 ml/kg cooled normal saline (4°C) over 30 to 60 minutes, followed by either surface or endovascular cooling to 34 to 35°C, maintained for 24 hours. Shivering and discomfort will be prevented and if necessary treated with anti-shivering drugs. All patients will receive best medical treatment, including intravenous thrombolysis with alteplase, if indicated.

Outcome measures

The primary outcome measure will be the common odds ratio of improvement on the modified Rankin Scale (mRS) at 90 days as analysed with multiple ordinal logistic regression (shift analysis). Raters will be blinded to treatment allocation. Secondary outcome measures include death and dependency (mRS > 2) at 90 days, infarct volume, quality of life, and serious adverse events.

Sample size

A trial with 750 patients per arm has 90% power to detect a 7% absolute improvement at the 5% significance level.

Data collection

Data will be collected to an electronic CRF. CT and MR images will be uploaded to this eCRF for distribution to the Core Imaging Team. Digital video (see below) will be uploaded to the eCRF for distribution to the outcome measures team. Blood samples will be allocated a unique identifier from the eCRF and will be collected nationally prior to forwarding to the Biomarkers Core Team.

Baseline

1. Date of birth, sex, and date and time of stroke onset;
2. Medical history and vascular risk factors;
3. Rectal temperature and oesophageal, tympanic, or bladder temperatures where available, blood pressure, and heart rate;
4. Pre-stroke scores on the mRS and Barthel Index (BI);
5. NIHSS;
6. Laboratory tests, including full blood count, serum glucose, electrolytes, INR, PTT, aPTT, and C-reactive protein;
7. Blood samples for analysis of biomarkers of brain injury and for genetic studies;
8. 12-lead electrocardiogram;
9. CT or MRI scan of the brain, depending on local preference.

Randomisation Through to Day 7 (± 1 day) or discharge, if earlier

1. Date and time of randomisation;
2. Date and time of start of cooling;
3. Level of consciousness, presence of shivering, rectal or bladder and tympanic temperatures, blood pressure, and heart rate every 15 minutes in the first three hours after start of cooling, and every 30 minutes thereafter until the end of the rewarming phase. Thereafter, blood pressure, heart rate, and tympanic temperature will be assessed every 8 hours until day 7 (or discharge, if earlier);
4. Laboratory tests, including full blood count, serum glucose, electrolytes, PTT, aPTT, C-reactive protein at 24 hours and at 3 days, blood samples for biomarker at 6, 12, 24, 48 and 96 hours, and 12-lead electrocardiogram at 6, 12, 24, and 48 hours after inclusion
5. NIHSS at 24 and 48 hours and at 7 days (or discharge, if earlier);
6. mRS and BI at day 7 (or discharge, if earlier);
7. Concurrent medication and other (stroke) treatment(s);
8. Neurological and systemic adverse events;
9. CT or MRI scan at day 5 ± 2 days;
10. Patient location (intensive care unit, high dependency unit, or Stroke Unit) on each day.

90 days (± 14 days)

1. Scores on the mRS, BI, and NIHSS. To promote objective outcome assessment, a trial nurse will perform a standardised evaluation of each patient, including functional status, which will be recorded as video. Equipment for this will be provided by the trial organisation. Based on this, an outcome committee blinded to treatment allocation will determine the scores on the mRS and BI;
2. Quality of Life data at day 90, based on the SF-36 Health Survey;
3. Patient location over the first 90 days after stroke;
4. Serious adverse events during the trial period from 7 days (or discharge, if earlier) through 90 days.