COOLing for Ischaemic Stroke Trial. A phase II randomised clinical trial.

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To compare the feasibility and safety of surface cooling to 34, 34.5, and 35*C, started within 4.5 hours after the onset of acute ischaemic stroke and maintained for 24 hours, in awake patients on a stroke unit.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Central nervous system vascular disorders
Study type	Interventional

Summary

ID

NL-OMON39710

Source
ToetsingOnline

Brief title
COOLIST: COOLing for Ischaemic Stroke Trial

Condition

- Central nervous system vascular disorders

Synonym
ischemic stroke; brain attack

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: Ministerie van OC&W,de Nederlandse Hartstichting.,Medivance

Intervention

Keyword: brain ischemia, cerebral stroke, clinical trial, induced hypothermia, phase II

Outcome measures

Primary outcome

Feasibility, defined as the number of patients that has successfully completed

the treatment strategy they had been assigned to.

Secondary outcome

The main secondary outcome measures include:

1. Time to target temperature;

2. Stability at target;

3. Complications;

4. Score on the modified Rankin scale at three months.

Study description

Background summary

Cooling to 32 - 34°C improves outcome in patients with post-anoxic encephalopathy after cardiac arrest. Animal studies strongly suggest that cooling also improves outcome after ischaemic stroke. In these studies, cooling was efficacious at temperatures of 35°C or below, with lower temperatures associated with a greater benefit. However, each further decrease in temperature may be tolerated less well by awake patients on a stroke unit. In contrast to endovascular cooling, surface cooling can probably be combined with concurrent thrombolysis. The feasibility of surface cooling to temperatures of 35°C or below in patients with acute ischaemic stroke has not been evaluated systematically in clinical studies.
Hypotheses: 1) Cooling to 34, 34.5,or 35°C by means of a surface cooling device, started within 4.5 hours after the onset of acute ischaemic stroke and maintained for 24 hours in awake patients on a stroke unit is safe. 2) In awake patients with ischaemic stroke, the feasibility of cooling decreases with each °C temperature reduction.

Study objective

To compare the feasibility and safety of surface cooling to 34, 34.5, and 35*C, started within 4.5 hours after the onset of acute ischaemic stroke and maintained for 24 hours, in awake patients on a stroke unit.

Study design

A randomised, open, multi-centre, phase II clinical trial with masked outcome assessment of functional outcome.

Intervention

Surface cooling to 34, 34.5, or 35°C maintained for 24 hours or standard treatment.

Study burden and risks

In non-randomised case series of patients with acute ischaemic stroke who were intubated and mechanically ventilated for cooling to 32 or 33°C, infections, arrhythmias, arterial hypotension, and thrombocytopenia were frequent complications. However, most of these complications may be attributed to the infarcts under study, which were generally severe, and to the intubation, sedation, and mechanical ventilation. In randomised trials of cooling to 32 to 34*C after cardiac arrest, no differences in adverse effects were observed between the hypothermia and control groups. In a case-control study of cooling to 35.5°C involving 17 patients with acute ischaemic stroke, a mild decrease in blood pressure and heart rate were observed during hypothermia, as well als mild increases in haematocrit and the concentrations of haemoglobin, potassium, creatinin, albumin, and C-reactive protein. No serious adverse events were observed.
In the NOCSS, cooling to 35°C was not associated with an increase in the numer of serious adverse events. Specifically, there was no indication of an increase in the occurrence of pneumonia.
In ICTuS-L, pneumonia occurred more often in patients treated with hypothermia (target: 33°C) than in controls (71 vs 29%), which may be caused by the high dose of pethidine used (starting dose, 1 mg/kg, followed by 30 mg/h), in combination with the severity of the strokes (mean baseline score on the NIHSS = 14). Symptomatic intracranial haemorrhage occurred in one of the patients treated with hypothermia and in three of the controls (no statistically significant difference). There was no difference between the groups in functional outcome at three months.

Hypothermia induces a mild bleeding diathesis, with increased bleeding time due to effects on platelet count, platelet function, the kinetics of clotting enzymes and plasminogen activator inhibitors, and other steps in the

coagulation cascade. Of note, hypothermia does not begin to affect platelet function until temperature decreases below 35°C; clotting factors are affected only when temperature decreases below 33°C. Despite the coagulation defects that can be caused by hypothermia, the risk of clinically significant bleeding induced by hypothermia in patients who are not already actively bleeding is very low. None of the large clinical trials in patients with TBI, subarachnoid hemorrhage, stroke, or postanoxic coma has reported significantly increased risks of bleeding associated with hypothermia.

Cooling without appropriate preventive measures leads to discomfort and shivering. To prevent and/or treat this, patients will be treated with intravenous pethidine and magnesium sulphate, and with oral buspirone.

Common side effects of pethidine are nausea, vomiting, constipation, drowsiness, and confusion. Other reported side effects include dry mouth, sweating, facial flush, vertigo, bradycardia, palpitations, orthostatic hypotension, hypothermia, restlessness, changes of mood, and hallucinations. At higher doses, respiratory depression, arterial hypotension, and a reduced consciousness have been reported. Due to the histamine-releasing effect, reactions such as urticaria, pruritus, as well as hypotension and flushing occur in some individuals.

The most common side effects of buspirone include light-headedness, headache, anxiousness, agitation, and nausea.

Patients in the cooling groups are given ondansetron to prevent and treat nausea. Ondansetron often (> 10%) gives rise to headache and (1 to 10%) constipation and a sensation of warmth. Occasionally (0.1 - 1%) seizures, movement disorders, chest pain with or without ST depression, arrhythmias, bradycardia, arterial hypotension, hiccup, and asymptomatic increase in hepatic enzymes have been reported.

Patients in the active treatment (= cooling) groups will have an additional (= second) intravenous line and continuous rectal thermometry during a maximum of 36 h from start of treatment. Cooling pads will be applied to the trunk and thighs for the same period of time. If required, e.g. because of severe nausea, a nasogastric tube will be inserted.

In all patients, the level of consciousness, presence of shivering, rectal temperature, blood pressure, and heart rate will be assessed every 15 minutes in the first two hours after start of treatment, every 30 minutes thereafter until 36 h after stroke onset, and every 6 h until day 7 (or discharge, if earlier). The presence and severity of shivering will be assessed at the same points in time. Tympanic temperatures will be assessed every 4 h during the first 48 h of treatment, and rectal temperature at 24 h.

Blood samples will be drawn at 90 min and at one and three days, and an ECG

will be performed at 12, 24, and 48 h after start of treatment. All patients will have a formal neurological examination at 24 and 48 h, and at one week and three months. Functional outcome will be assessed with the modified Rankin Scale and the Barthel Index at one week (or at discharge, if earlier) and at three months. At one week (or at discharge, if earlier), all patients will be interviewed about discomfort during the first two days of treatment. As in all patients with acute ischaemic stroke, a CT or MRI scan of the brain will be performed at about 3 days.

The additional efforts for patients in the control group appear justified as these are small in comparison with standard care after intravenous thrombolysis. The efforts and risks for patients in the active treatment group are larger (the cooling itself and the medication to prevent shivering and discomfort), but may be compensated by the potential benefit of treatment. All patients have a moderately severe or severe ischaemic stroke, for which no other treatment with proven benefit than intravenous thrombolysis is currently available.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. A clinical diagnosis of acute ischaemic stroke;
2. A possibility to initiate cooling within 4.5 hours of stroke onset. Onset time for patients who awoke with symptoms is defined as the last time the patient was awake without symptoms of stroke;
3. Score on the National Institutes of Health Stroke Scale (NIHSS) >= 6;
4. Age >= 18 years;
5. Written informed consent by the patient or a legal representative.

Exclusion criteria

1. Evidence from a CT or MRI scan or from other pre-randomisation investigations of an intracranial haemorrhage, a brain tumour, encephalitis, or any diagnosis other than acute ischaemic stroke likely to be the cause of the 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 complicated by hypothermia, such as haematological dyscrasias(including oral anticoagulant treatment with INR >=1.7 or a platelet count < 100.10exp9/L), severe pulmonary disease, severe heart failure (defined as a NYHA score of III or IV), myocardial infarction within the previous 3 months, angina pectoris in the previous three months, severe infection with a CRP > 50 mg/L, or a clinical diagnosis of sepsis;
3. Blood oxygen saturation below 92% without use of oxygen therapy or below 94 % with a maximum of 2 L/min oxygen delivered nasally;
4. Bradycardia (<40 beats/min);
5. Body weight > 120 kg;
6. Pre-stroke score on the modified Rankin Scale (mRS) > 2;
7. Allergy to pethidine or buspirone, use of a monoamine oxidase inhibitor in the previous 14 days, hepatic or severe renal dysfunction, or asthma. Severe hepatic dysfunction is defined as liver enzymes increased above two times above the upper limit of normal, and severe renal dysfunction as a glomerular filtration rate <= 30 ml/min.;
8. Pregnancy. Women of childbearing potential are excluded unless a negative test for pregnancy has been obtained prior to randomization;
9. Other serious illness that may confound treatment assessment;
10. Previous participation in this trial.

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Other
Allocation:	Randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	28-10-2011
Enrollment:	48
Type:	Actual

Medical products/devices used

Generic name:	Arctic Sun cooling device
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	12-04-2011
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	13-08-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL32092.041.10