

MASCOT – Malmö Acute Stroke Cooling Trial

Background

In Sweden, 30 000 persons a year will experience a stroke. It's one of the most common and costly causes of death and disability. It is well-known that early treatment with the help of established guidelines improves the outcome after stroke. However, many patients still have a severe deficit with a deleterious impact on quality of life. Evidence based treatment includes specialized stroke units, early mobilisation and, for some patients, acute thrombolytic treatment. It has been shown that with stroke unit treatment alone 22% more patients will recover to an independent life, compared to treatment on a non-specialized ward.

There is extensive evidence from animal studies, showing that hypothermia will have a favourable effect on many of the different consequences of cerebral ischemia, i.e. edema, lactic acidosis, calcium release, free radicals, apoptosis, inflammation and release of excitotoxic neurotransmitters. Mild hypothermia, defined as body core temperature of 32-35°C, is used to protect the brain of cardiac arrest victims. This treatment is used in an increasing number of countries in Europe and notably Scandinavia. As suggested by two pivotal studies, after cardiac arrest and resuscitation the patient is actively cooled to 33°C and this temperature level is kept for 24 hours. Cooling has so far been tried on stroke-patients in a few and relatively small studies and has not yet become a standard treatment option.

The time-window for acute stroke treatment in stroke varies from 48 hours down to just 1 hour in the literature. Today we know that thrombolytic treatment is beneficial up to three hours after the stroke but that some patients may benefit up to six hours after the onset of stroke. Some patients fluctuate in their clinical status up to a week after the initial stroke suggesting that there is a considerable amount of brain tissue that is a potential target for neuroprotective treatment. Recent studies of neuroprotective drugs have used a three day treatment regimen in order to cover as much of the presumed penumbra period as possible.

Hypothermia has many different biological effects on the brain and the exact mechanism for its positive role in treatment of brain disease is not known. More effort is needed to look in to physiologic changes that occur during acute ischaemia and the influence of cooling.

Study design

Randomised controlled study where patients are given hypothermia treatment or standard stroke unit treatment.

Number of patients: 2 x 20

Main objective:

The present study addresses patients that do not improve in spite of standard treatment in a dedicated stroke unit. It is important to find new treatment possibilities for this group of patients since they tend to do worse, in both morbidity and mortality.

Primary endpoint:

Safety and feasibility, defined as morbidity and mortality at 30 days after stroke onset.

Secondary endpoints:

Modified Rankin Scale at 7 days

Modified Rankin Scale at 3 months

Qualitative evaluation of EEG-monitoring at 24 hours and during rewarming

Levels in serum of brain injury markers (S-100 and NSE at 4, 12, 16, 18, 24 and 48 hours)

Levels in serum of narcotic drugs used for sedation during cooling period and after rewarming

Transcranial Doppler after start of cooling (0-2 hours + 12 hours) and after rewarming

Inclusion criteria:

Patient admitted and treated for ischaemic stroke at the stroke unit.

Patient with NIHSS-score of 4-18

0-24 h after stroke onset

Confirmation of stroke diagnosis with MRI or CTP

Worsening or lack of improvement as measured with NIHSS after 3 hours of stroke unit care compared to score at admission

Patients who receive rTPA but do not improve after infusion may be randomized

Age ≥ 18

Informed consent from patient, next of kin or other legally accepted representative

Exclusion criteria:

Disability more than mRS (modified Rankin scale) 2 prior to actual stroke

Patients with signs of malignant media infarction or hemorrhagic stroke. Small ($< 0,5$ cm) petechiae in the area of infarction are allowed.

Patients on anticoagulation medication with an INR above 1.2, serious heart disease, serious lung disease, malignancy or other serious disease

Description of treatment:

All patients will be treated at Malmö University Hospital. Patients randomized to mild hypothermia treatment will be transferred to the ICU where the patient will be sedated and anesthetized (Propofol 1 mg/kg/h, fentanyl 0.1 ug/kg/h), intubated and mechanically ventilated prior to and during hypothermia at 33°C for 24 hours according to standard protocol used for cardiac arrest victims.

Monitoring

Physiologic parameters will be monitored according to ICU standards. A 5-channel continuous EEG-recording will be performed every 4 hours. Transcranial Doppler (TCD) examination will be performed at least once during the cooling phase, during the rewarming procedure and after achieved normothermia. Blood samples for brain damage markers will be taken at initiation of treatment, every 4 hours over the first 24 hours, and once daily for two more days. Blood samples for determination of the concentration of sedatives will be obtained during cooling, hypothermia and rewarming. At 7 and 90 days post treatment an evaluation will be performed, NIH-stroke scale, CPC and modified Rankin test. At 30 days post treatment mortality, AE's and SAE's will be recorded.

Patients randomized to standard treatment will be evaluated in the same way with the exception of the blood samples taken for analysis of sedatives. TCD will be performed at 2 h, 12 h, 28 h and 48 h in this group.

Basic treatment protocols for blood sugar levels and changes in blood pressure will be harmonized for both groups with respect to treatment levels and drug regimens.

BioBank

Blood samples will be obtained as described above. Some of the samples will be saved since it is possible that testing for new brain damage markers will be possible in the future. Informed consent will be obtained for collection and handling of blood samples. The samples will be kept at UMAS according to present routines and destroyed if the patient withdraws consent.

Local experience

Mild hypothermia is an established treatment in the Malmö ICU for cardiac arrest patients. The Malmö Stroke Unit has participated in the first multicenterstudy (NOCSS) treating stroke patients with hypothermia. Hence, there is a well established know-how in the two units for hypothermic treatment.

Power

A feasibility study should have a low number of patients since it aims to determine the safety of the treatment. To use a control group will give better evidence than comparison with historical data.

Risk-benefit

The hypothermia treatment protocol described above is well-proven in cardiac arrest patients and considered to be a safe procedure. Hypothermia might result in increased neuroprotection for treated patients, something which may outweigh possible risks added by hypothermia. Patients in the control group will be closely monitored which might be beneficial.

Ethics

Approval from the regional ethics committee is mandatory before start of the study.

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