THERAPEUTIC COOLING FOR ACUTE ISCHEMIC STROKE

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Cooling for focal ischemia: Does it enhance outcomes for stroke?

Animal experiments on intraischemic hypothermia for focal ischemia began in the 1950's. Rosomoff reported in 1956 that dogs who were cooled to 22-24ºC (profound hypothermia) and then had permanent interruption of one middle cerebral artery, had significantly better neurobehevioral outcome than normothermic controls (Rosomoff et al 1956). Xue et al more recently reported a study of rats that were cooled to 32ºC (moderate hypothermia) and then received either permanent or transient focal ischemia. The hypothermic rats that received permanent focal ischemia had a 60% reduction in infarct size compared with normothermic controls; the rats who received transient focal ischemia had a 92% reduction in infarct size compared with normothermic controls (Xue et al 1992). This same study also demonstrated that rats with delayed initiation of hypothermia, up to 90 minutes after onset of occlusion, had significantly smaller infarct volumes than normothermic controls. The benefit was greater with prolonged periods of post-ischemic hypothermia (49-73% reduction). Baker et al had similar results in rats using cooling to 24ºC up to one hour postischemia (Baker et al 1992). Others have shown that even minute changes in brain temperature by only 1-2^{o} C confer protection (Ginsberg et al 1992, 1994). 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.

Conversely, in humans, it has been suggested that slight reductions in body temperature may confer benefit in acute stroke patients (Kammersgaard et al 2000). Obviously, these pilot results need to be evaluated in large controlled studies. There have been several clinical feasibility trials of moderate hypothermia for massive ischemic stroke. The first, published in 1998 by Schwab et al, was a report of 25 patients with severe MCA infarction. The mean time from onset of symptoms to initiation of hypothermia was 14 hours, after which patients required 3.5-6.2 hours to achieve a target of 32-33ºC using surface cooling methods (Schwab et al 1998). Fifty-six percent of patients survived; herniation related to cerebral edema during rewarming was a prominent complication, being responsible for all of the mortalities. Among the survivors, the median Scandinavian Stroke Scale was 29 after 4 weeks, and 38 after 4 months; the median Barthel Index was 70 and the mean Rankin scale was 2.6. The second feasibility trial was the Cooling for Acute Ischemic Brain Damage (COOL AID) open pilot study, published in 2001 (Krieger et al 2001). Hypothermia, using surface cooling, was induced in 10 patients who suffered massive infarction. It was initiated at a mean of 6.2+/-1.3 hours after stroke onset, and patients arrived at the target 32ºC at a mean of 3.5 +/- 1.5 hours after initiation of cooling. Although not randomized, this study utilized concomitant patients with severe strokes that underwent thrombolysis but not hypothermia as a control group. Three-month neurologic outcomes using the modified Rankin scale were better in the hypothermia group, although these numbers did not reach statistical significance. The follow up COOL AID II has been completed suggesting similar benefit with endovascular cooling (DeGeorgia et al 2004). The difference between the two approaches is a shift of objective. Schwab et al targeted ischemic brain edema associated with massive strokes, whereas the COOL AID series tested the feasibility of adjunctive hypothermia in the setting of patients with severe stroke undergoing thrombolytic therapy. The COOL AID study is the first study to address hypothermia in the late ischemic/early post-ischemic phase in humans. COOL AID was conducted in a neurocritical care environment while COOL AID II was conducted in non-intubated patients in a stroke unit. While in COOL AID no major complications were noted, the application of therapeutic cooling in regular care units is associated with complications, mainly aspiration and pneumonia. Others have recently replicated these concerns (Hemmen et al 2010). The fundamental problem of therapeutic cooling for patients with acute ischemic stroke is to find a balance between the benefits and medical complications associated with therapeutic cooling.

Clinical Trials testing therapeutic cooling in ischemic stroke are ongoing.

The EuroHYP consortium and the ICTUS investigators have received funding by the FP-7 programme of the European Union and the National Institute of Health to conduct phase III studies to evaluate the benefit of therapeutic cooling for stroke.

The EuroHYP-1 study is designed to determine whether systemic cooling to a target temperature of 34 to 35°C of awake patients, started within 6 hours of symptom onset and maintained for 24 hours, improves functional outcome at 3 months in patients with acute ischaemic stroke. 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.

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 (figure 1). 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.

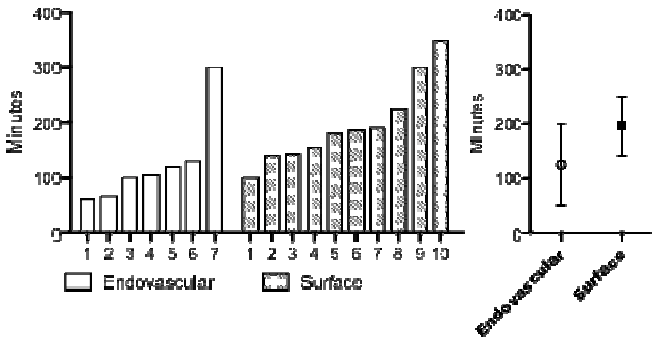

Figure 1: Left graph shows individual patients' induction period. Right figure shows mean induction period (±95% CI) for the two different cooling modalities (P=0.025). This figure is taken from Ovensen et al 2012 (in preparation)

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.

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