Ranadhir Mitra

Piironen, Katja, Marjaana T, Mustanoja S, Kirsi-Maija K, Atte M, *et al*. Mild hypothermia after intravenous thrombolysis in patients with acute stroke a randomised controlled trial. Stroke 2014;45:486-91.

Although hypothermia has been used in multiple clinical settings, it has proven neuroprotective effect in clinical trials of global cerebral ischaemia for cardiac arrest and newborn hypoxic encephalopathy.[1,2] In the era preceding thrombolysis, following the prospective, observational analysis of the Copenhagen Stroke Study Registry that for each 1°C increase in body temperature at admission after acute stroke, the relative risk of poor outcome rose by 2.23.[3] Kammersgaard *et al*.,[4] conducted a feasibility and safety trial of hypothermia for stroke patients. Seventeen patients (cases) with stroke admitted within 12 hours from stoke onset (mean 3.25 hours) were given hypothermic treatment for 6 hours by the "forced air" method (surface cooling) with antishivering medication Pethidine. Cases were compared with 56 matched patients (controls) from the Copenhagen Stroke Study. Mortality at 6 months after stroke was 12% in cases versus 23% in controls. Final neurological impairment (Scandinavian Stroke Scale score at 6 months) was mean 42.4 points in cases versus 47.9 in controls. Authors concluded that induced hypothermia was not associated with poor outcome, death, or an increased incidence of infectious complications with shivering being the most common adverse event. This study went to spawn all further studies investigating hypothermic neuroprotection in acute stroke.

The current study by Piironen *et al*., a randomised controlled trial from Helsinki University Central Hospital was undertaken to study the safety and feasibility of mild hypothermia in awake patients with stroke who have already received intravenous thrombolysis. Patients were randomised to mild hypothermia (35°C) or to standard stroke unit care within 6 hours of symptom onset. Hypothermia was induced with a surface-cooling device and cold saline infusions (core cooling). Active cooling was stopped gradually after 12 hours at <35.5°C. The primary outcome measure was the number of patients with <36°C body temperature for >80% of the 12-hour cooling period. They included 36 patients with a median of National Institutes of Health Stroke Scale (NIHSS) score of 9, 1 hour after thrombolysis. Fifteen of 18 (83%) patients achieved the primary end point. Sixteen (89%) patients reached <35.5°C in a median time of 10 hours (range, 7-16 hours) from symptom onset, spent 10.5 hours (1-17 hours) in hypothermia, and were back to normothermia in 23 hours (15-29 hours). Adverse events though few were more common in the hypothermia group. At 3 months, 7 patients (39%) in both groups had good outcome (modified Ranking Scale, 0-2), whereas poor outcome (modified Ranking Scale, 4-6) was twice more common in the normothermia group (44% versus 22%). Based on the rarity of adverse events and better outcome profile at 3 months the authors concluded that mild hypothermia with a surface-cooling device in an acute stroke unit is safe and feasible in awake patients with stroke.

After arrival of alteplase, concerns regarding the risk of intracerebral haemorrhage because of hypothermia-induced thrombocytopenia and coagulopathy were addressed by the COOL AID I trial.[5] They recruited 19 patients with NIHSS score of >15) who received alteplase for thrombolysis. Ten patients were subjected to hypothermia (via surface cooling) and nine patients served as controls. Hypothermia was implemented within 6.2 ± 1.3 hours of symptom onset. Cooling to a core temperature of 32°C was achieved in 3.5 ± 1.5 hours. Adverse events were more common in the hypothermia group but mean modified Rankin Scale scores were 3.1 ± 2.3 at 3 months, versus 4.2 ± 1.6 in non hypothermic patients. This trial went on to prove the feasibility and safety of combining thrombolytic therapy and hypothermia in patients with acute ischaemic stroke.

The Intravascular Cooling for the Treatment of Stroke-Longer window (ICTuS-L)[6] further investigated the feasibility and safety of intravenous alteplase combined with intravascular cooling. The trial included 59 patients divided into two cohorts. The first cohort

Access this article online	
Quick Response Code:	Website: www.jnaccjournal.org
	DOI: 10.4103/2348-0548.130416

Department of Neuroanesthesiology, All India Institute of Medical Sciences, New Delhi, India

Address for correspondence:
Dr. Ranadhir Mitra, Department of Neuroanaesthesiology, Neurosciences Centre, All India Institute of Medical Sciences, New Delhi - 110 029, India. E-mail: ranadhir.mirtra@gmail.com

included patients who presented within 3 hours of symptom onset who received the standard dose of intravenous alteplase, and were then randomised to therapeutic hypothermia or standard medical care. The second cohort of patients presented at 3-6 hours of onset and was randomised to four groups as follows: no treatment, treatment with alteplase only, treatment with hypothermia only or combined therapy. The hypothermia protocol included endovascular cooling for 24 hours and controlled rewarming for 12 hours. Because of technical difficulties, hypothermia was not achieved in two of 28 patients randomised to cooling groups. Although the incidence of pneumonia was higher in the hypothermia groups, there were no statistically significant differences in outcome or death at 3 months among the groups.

There are two other ongoing trials addressing the same issue of therapeutic efficacy of hypothermia. The ICTuS 2/3 study has a projected enrolment of 1600 patients and aims to establish whether the combination of thrombolysis and therapeutic hypothermia (Endovascular catheter cooling to a target temperature of 33°C) is superior to thrombolysis alone in acute ischaemic stroke. The target time for catheter placement is within 2 hours of completion of the intravenous alteplase infusion, followed by cooling for 24 and 12 hours of rewarming. The primary outcome measure of ICTuS 2/3 is favourable outcome defined as a 90-day modified Rankin scale score of 0 or 1, with secondary outcomes of 90-day NIHSS, Barthel Index score, modified Rankin scale score, mortality, incidence of symptomatic intracranial haemorrhage, adverse events and serious adverse events.

The EuroHYP-1 is a European prospective open, randomised controlled phase 3 clinical trial with projected enrolment of 1500 awake patients with cooling to a target temperature of 34-35°C with either surface or endovascular cooling devices for 24 hours. Patients presenting within 6 h of stroke onset are eligible for entry, with cooling initiated within 90 min of alteplase administration or 90 min of hospital admission in alteplase-ineligible patients. The primary outcome measure is improvement in the 90-day modified Rankin scale score, with secondary outcome measures of death and dependency at 90 days, infarct volume, quality of life and serious adverse events.

REFERENCES

1. Hypothermia after Cardiac Arrest Study Group. Mild therapeutic hypothermia to improve the neurologic outcome after cardiac arrest. N Engl J Med 2002;346:549-56.
2. Shankaran S, Laptook AR, Ehrenkranz RA, Tyson JE, McDonald SA, Donovan EF, *et al.* National Institute of Child Health and Human Development Neonatal Research Network. Whole-body hypothermia for neonates with hypoxic-ischaemic encephalopathy. N Engl J Med 2005;353:1574-84.
3. Reith J, Jørgensen HS, Pedersen PM, Nakayama H, Raaschou HO, Jeppesen LL, *et al.* Body temperature in acute stroke: Relation to stroke severity, infarct size, mortality, and outcome. Lancet 1996;347:422-5.
4. Kammersgaard LP, Rasmussen BH, Jørgensen HS, Reith J, Weber U, Olsen TS. Feasibility and safety of inducing modest hypothermia in awake patients with acute stroke through surface cooling: A case-control study: The Copenhagen Stroke Study. Stroke 2002;31:2251-6.
5. Krieger DW, De Georgia MA, Abou-Chebl A, Andrefsky JC, Sila CA, Katzan IL, *et al.* Cooling for acute ischemic brain damage (cool aid): An open pilot study of induced hypothermia in acute ischemic stroke. Stroke 2001;32:1847-54.
6. Hemmen TM, Raman R, Guluma KZ, Meyer BC, Gomes JA, Cruz-Flores S, *et al.* ICTuS-L Investigators. Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): Final results. Stroke 2010;41:2265-70.

Hong, Ji M, Jin SL, Hee-Jung S, Hye SJ, Huimahn AC, *et al.* Therapeutic hypothermia after recanalisation in patients with acute ischaemic stroke. Stroke 2014;45:134-40.

Hypothermia attenuates neuronal damage in the injured brain by affecting varied pathways activated due to ischaemia. These include energy depletion, ion shifts, free radical formation, EAA release and inflammation.[1] Cerebral oxygen consumption is reduced at a rate of approximately 6% per 1°C decrease in temperature, allowing reduced oxidative debt in times of ischaemia. This, in turn, maintains ionic homeostasis and prevents release of ischaemia-induced excitatory amino acids, free radicals and inflammatory responses which can increase recruitment of ischaemic penumbra.

Hong *et al.*, carried out a prospective cohort study at two stroke centres to investigate the clinical and radiological effects of therapeutic hypothermia in acute ischaemic stroke patients after recanalisation. They enrolled patients with acute ischaemic stroke of the anterior circulation with an initial National Institutes of Health Stroke Scale (NIHSS) ≥10 who had successful recanalisation (i.e., thrombolysis in cerebral ischaemia). Patients at one centre underwent a mild hypothermia (34.5°C) protocol, which included mechanical ventilation, and 48-hour hypothermia and 48-hour rewarming while patients at the other centre were treated according to the guidelines without hypothermia. Cerebral oedema, haemorrhagic transformation, good outcome (3-month modified Rankin Scale, ≤2), mortality and safety profiles were compared. All potential variables were analyzed before and after initiating intervention. The hypothermia group (n = 39) had less cerebral oedema (P = 0.001), haemorrhagic transformation (P = 0.016) and better outcome (P = 0.017) compared with the normothermia group (n = 36). Mortality, haemicraniectomy rate and medical complications were comparable in both