

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.<sup>[1]</sup> 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)  $\geq 10$  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,  $\leq 2$ ), 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

the groups. The authors concluded that in patients with ischaemic stroke, after successful recanalisation, therapeutic hypothermia may reduce the risk of cerebral oedema and haemorrhagic transformation and may lead to improved clinical outcomes. This study is different for reasons like prolonged use of hypothermia (48 hours), compulsory mechanical ventilation and stress on post-recanalisation ischaemia reperfusion complications.

In 2007, van der Worp *et al.*,<sup>[1]</sup> carried out a systemic review and meta-analysis of the evidence for efficacy of hypothermia in animal models of ischaemic stroke in which 101 publications reporting the effect of hypothermia on infarct size or functional outcome, including data from a total of 3353 animals were taken into account. Overall, hypothermia reduced infarct size by 44%. Efficacy was highest with cooling to lower temperatures ( $\leq 31$  degree and started before or at the onset of ischaemia in temporary ischaemia models). However, a substantial reduction in infarct volume was also observed with cooling to 35 degree with initiation of treatment between 90 and 180 min and in permanent ischaemia models. The effects of hypothermia on functional outcome were broadly similar and hence the authors concluded that in animal models of focal cerebral ischaemia, hypothermia improves outcome.

The improvement in cranial imaging and functional outcome after institution of hypothermia has also been corroborated in the Kollmar *et al.*, study.<sup>[2]</sup> Here 12 patients with supratentorial sICH (spontaneous intracerebral haemorrhage)  $>25$  ml were treated by hypothermia of 35°C for longer duration of 10 days. Evolution of haematoma volume and perifocal oedema was measured by cranial CT and functional outcome was assessed after 90 days. The control group comprised patients ( $n = 25$ ; inclusion criteria: sICH volume  $>25$  ml with no acute restriction of medical therapy on admission) from the local haemorrhage data bank ( $n = 312$ ). All hypothermic patients survived until day 90, whereas seven patients died in the control group). Also in the hypothermia group, oedema volume remained stable during 14 days whereas oedema significantly increased in the control group from  $40 \pm 28$  ml (day 1) to  $88 \pm 47$  ml (day 14). The incidence of pneumonia was 100% in the hypothermia group and 76% in control group. The authors concluded that hypothermia prevented an increase of peri-haemorrhagic oedema in patients with large sICH.

At present there is no consensus regarding duration of hypothermia to be instituted for neuroprotection in acute ischaemic stroke. Jiang *et al.*,<sup>[3]</sup> carried out a comparative study between long versus short duration of hypothermia in severe traumatic brain injury (TBI). Two-hundred and fifteen patients aged 18-45-years old with an admission Glasgow Coma Scale  $\leq 8$  within

4 h after injury were randomly divided into two groups: long-term mild hypothermia group ( $n = 108$ ) for  $5 \pm 1.3$  days and short-term mild hypothermia group ( $n = 107$ ) for  $2 \pm 0.6$  days of mild hypothermia therapy. They found similar rate of adverse events in both the groups while improved outcome in the hypothermia group.

## REFERENCES

1. van der Worp HB, Sena ES, Donnan GA, Howells DW, Macleod MR. Hypothermia in animal models of acute ischaemic stroke: A systematic review and meta-analysis. *Brain* 2007;130:3063-74.
2. Kollmar R, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J. Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke* 2010;41:1684-9.
3. Jiang JY, Xu W, Li WP, Gao GY, Bao YH, Liang YM, *et al.* Effect of long-term mild hypothermia or short-term mild hypothermia on outcome of patients with severe traumatic brain injury. *J Cereb Blood Flow Metab* 2006;26:771-6.

**Hougaard KD, Niels H, Dora Z, Leif S, Anne N, Troels MH, *et al.* Remote ischaemic preconditioning as an adjunct therapy to thrombolysis in patients with acute ischaemic stroke a randomised trial. *Stroke* 2014;159-67.**

Preconditioning is a procedure by which a noxious stimulus near to but below the threshold of damage is applied to the tissue through which the organ (and therefore the organism) develops resistance to, or tolerance of, the same, similar or even different noxious stimuli given beyond the threshold of damage thereby conferring protection. Ulrich Dirnagl *et al.*,<sup>[1]</sup> in their review article published in *Lancet Neurology* dwells on the mechanisms of ischaemic preconditioning and its possible clinical uses. Basically sub-threshold ischaemia protects through four ways which are increased substrate delivery (via angiogenesis), metabolic downregulation through gene modulation, antagonism of damaging pathways (downregulation of NMDA and AMPA receptors) and improved recovery by stimulating progenitor cells in the subventricular zone of the lateral ventricles and the subgranular zone in the hippocampal dentate gyrus.

The current study by Hougaard *et al.*, is an open-label blinded outcome proof-of-concept study of prehospital, paramedic-administered remote ischaemic preconditioning through (rPerC) intermittent upper arm ischaemia in patients with suspected acute stroke. Post-neurological examination and MRI, patients with verified stroke receiving alteplase treatment were included and had MRI at 24 hours and 1 month and clinical re-examination after 3 months. The primary end point was penumbral salvage, defined as the volume of