

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.*,^[1] 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 (≤ 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.^[2] 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+/- 28 ml (day 1) to 88+/- 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.*,^[3] 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 ≤ 8 within

4 h after injury were randomly divided into two groups: long-term mild hypothermia group ($n = 108$) for 5+/- 1.3 days and short-term mild hypothermia group ($n = 107$) for 2+/- 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.

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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.*,^[1] 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

the perfusion-diffusion mismatch not progressing to infarction after 1 month. Four hundred and forty-three patients were enrolled out of which 247 received rPerC while 196 had standard treatment. Transient ischaemic attack was more frequent ($P = 0.006$), and NIHSS on admission was lower ($P = 0.016$) in the intervention group compared with controls. Although penumbral salvage, infarct growth and size at 1 month, and clinical outcome after 3 months did not differ among groups but the authors concluded that prehospital rPerC may have immediate neuroprotective effects.

Hahn *et al.*,^[2] carried out the first study showing the effectiveness of preconditioning as a neuroprotective strategy. Thirty nine male P60 Sprague-Dawley rats were randomly allocated to three groups: a control group, which received no intervention, a preconditioning group through transient limb ischaemia 40 minutes before surgery and a per-conditioning group where it was initiated 40 minutes before reperfusion. Focal cerebral ischaemia was achieved using transient right middle cerebral artery occlusion, performed surgically under isoflurane anaesthesia. The resulting infarct size at 24 hours was quantified using computerised image analysis of 2-3-5-triphenyl tetrazolium chloride-stained brain sections. It was observed that compared with control, preconditioning significantly reduced brain infarct size with the more clinically relevant per-conditioning stimulus being superior to preconditioning. The authors concluded that remote per-conditioning by transient limb ischaemia provides potent neuroprotection in a model of regional brain ischaemia-reperfusion injury.

In 2012 Meng *et al.*,^[3] studied the protective effectiveness of brief repetitive bilateral arm ischaemic preconditioning (BAIPC) on stroke recurrence in patients with symptomatic atherosclerotic intracranial arterial stenosis (IAS). Sixty-eight patients were enrolled with symptomatic IAS, diagnosed by imaging in this prospective and randomised study. All patients received standard medical management. Patients in the BAIPC group ($n = 38$) underwent five brief cycles consisting of bilateral upper limb ischaemia followed by reperfusion.

The BAIPC procedure was performed twice daily over 300 consecutive days. Incidence of recurrent stroke and cerebral perfusion status in BAIPC-treated patients were compared with the untreated control group ($n = 30$). In the control group, incidence of recurrent stroke at 90 and 300 days were 23.3% and 26.7%, respectively. In the BAIPC group, incidence of recurrent stroke was reduced to 5% and 7.9% at 90 and 300 days ($P < 0.01$), respectively. The average time to recovery (modified Rankin Scale score 0-1) was also shortened by BAIPC. Cerebral perfusion status, measured by SPECT and transcranial Doppler sonography, improved remarkably in BAIPC-treated brain than in control ($P < 0.01$). It was concluded that BAIPC may be an effective way to improve cerebral perfusion and reduce recurrent strokes in patients with IAS.

A Cochrane database review^[4] in 2011 on remote ischaemic preconditioning versus no remote ischaemic preconditioning for vascular and endovascular surgical procedures conclude insufficient data at present to say whether remote ischaemic preconditioning has any beneficial or harmful effects. There is a need for further randomised trials on this technique to give shape to definite therapeutic guidelines.

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