

DEBATE: IS HYPOTHERMIA EFFECTIVE AS ADD ON THERAPY IN ACUTE STROKE? – NO

Erich Schmutzhard

Department of Neurology, Neurocritical Care Unit (NICU), Innsbruck, Austria

Ischemic stroke is a rapidly developing loss of brain function due to impairment of brain supply from ischemia caused by thrombosis, arterial embolism or hemorrhage. Ischemic stroke represents up to 80 % of the total stroke burden, stroke being the leading cause of adult disability and third leading cause of death in North America and Europe.

One of the gold standards of neuroprotective therapies against ischemic stroke in animal experiments is induced mild to moderate hypothermia. In the past decade, prospective randomized controlled studies have demonstrated that induced hypothermia improves neurological function in patients suffering from cardiac arrest due to ventricular fibrillation and it reduces risk of death and disability in neonates following hypoxic-ischemic encephalopathy. The pathophysiological processes are grossly regarded to be similar in hypoxic encephalopathy and ischemic stroke, thus rendering the extremely frequent disease of cerebral ischemia (= ischemic stroke) a potential target for this type of neuroprotective therapy. Extrapolating animal studies to human patients, however, significant gaps exist between the design of laboratory experiments and clinical trials. For example, in most animal models complete reperfusion is allowed / used, while ischemic stroke patients frequently suffer from permanent cerebral artery occlusion even in the context of rTPA treatment, where less than one third of patients achieve a complete reperfusion; even more ominous, the rTPA treatment is used in less than 15% of ischemic stroke patients in the best of all circumstances.

With respect to ischemic stroke the published literature contains no randomized controlled trial sufficient to support or to be an assertion that therapeutic hypothermia or, as recently suggested, targeted temperature management may be of benefit. Whether targeted temperature management – as adjunctive therapy – would further improve the outcome in ischemic stroke patients is speculative. However, it has been shown that the introduction of therapeutic hypothermia/targeted temperature management has the potential to increase the rate of pneumonia, may be even the need for endotracheal intubation and mechanical ventilation, thus carrying the risk to harm these frequently multi- morbid ischemic stroke patients. Therefore such a risk for harm needs to be addressed in any clinical trial. This assumption is underlined by the findings of a Chinese group that local mild hypothermia together with thrombolysis for acute ischemic stroke (carried out all together within a 6 hour window) is not superior to intravenous rTPA alone. The outcome criteria were evaluated at 24 hours and 90 days after i.v. rTPA treatment had begun. Low body temperature does not compromise the treatment effect of rTPA, improved outcome has been observed at temperatures between 35,5 und 37,5°C whereas significance had been lost at temperatures <35,5° and >37,5°.

Whether targeted temperature management conveys a benefit to the most severe stroke patients, i. e. with malignant A. cerebri media infarction, even as a postoperative add on therapy (after decompressive craniectomy) needs to be evaluated.

Very recently targeted temperature management has been used in a small case series with hemorrhagic stroke (intracerebral hemorrhage - ICH). In these patients the freezing of the perihemorrhagic edema has been shown in 10 consecutive ICH patients.

Currently, several prospective randomized trials have been initiated, just to name: IctUS 2 and IctUS 3 for ischemic Stroke and CINCH for hemorrhagic Stroke to study the feasibility, safety and, in the long run, also efficacy of targeted temperature management (therapeutic hypothermia) in stroke patients.

Literature

Broessner G, Beer R, Lackner P, et al (2009). Prophylactic, endovascularly based, long-term normothermia in ICU patients with severe cerebrovascular disease: bicenter prospective, randomized trial. *Stroke*; 40:e657-665

Broessner G, Lackner P, Fischer M, et al (2010). Influence of prophylactic, endovascularly based normothermia on inflammation in patients with severe cerebrovascular disease: a prospective, randomized trial. *Stroke*; 41:2969-2972

De Georgia M, Patel V (2011). Critical care management in acute ischemic stroke. *J Neurointerv Surg*; 3:34-37

Di Lazzaro v, Profice P, Dileone M, et al (2011). Delayed hypothermia in malignant ischaemic stroke. *Neurol Sci [Epub ahead of print]*

Bi M, Ma Q, Zhang S, et al (2011). Local mild hypothermia with thrombolysis for acute ischemic stroke within a 6-h window. *Clin Neurol Neurosurg*; 113:768-773

Bernard SA (2011). Targeted temperature management: the jury returns with a verdict (2011). *Crit Care Med*; 39:1226-1228

Fischer M, Dietmann A, Lackner P, et al (2011). Endovascular Cooling and Endothelial Activation in Hemorrhagic Stroke Patients. *Neurocrit Care [Epub ahead of print]*

Hemmen TM, Raman R, Guluma KZ, et al (2010). Intravenous thrombolysis plus hypothermia for acute treatment of ischemic stroke (ICTuS-L): final results. *Stroke*; 41:2265-2270

Kollmar R, Staykov D, Dörfler A, Schellinger PD, Schwab S, Bardutzky J (2010). Hypothermia reduces perihemorrhagic edema after intracerebral hemorrhage. *Stroke* 41:1684-1689

Nunnally ME, Jaeschke R, Bellingan GJ, et al (2011). Targeted temperature management in critical care: a report on recommendations from five professional societies. *Crit Care Med*; 39: 1113-1125

Zgavc T, Ceulemans AG, Sarre S, Michotte Y, Hachimi-Idrissi S (2011). Experimental and clinical use of therapeutic hypothermia for ischemic stroke: opportunities and limitations. *Stroke Res Treat*; 2011:689290 [Epub 2011 Jul 12]