The management of acutely ruptured intracranial aneurysms

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The management of intracranial aneurysms rests on two major therapeutic strategies, which can be either reconstructive or deconstructive in nature. Reconstructive treatment strategies result in selective aneurysm occlusion without impairment of parent artery patency. Such strategies include both microsurgical clipping and endovascular coil embolisation as well as stent and balloon supported embolisation. In the clinical setting of hemorrhagic stroke from intracranial aneurysm rupture, the results of the ISAT trial still indicate advantages of endovascular over microsurgical aneurysm occlusion in cases of clinical equipoise. In contrast, deconstructive treatment strategies aim for aneurysm occlusion in conjunction with therapeutic parent artery sacrifice. Such procedures may be performed as parent artery occlusion alone or in conjunction with protective bypass surgery. In selected cases, flow reversal and flow modification techniques may be performed. In view of the multitude of therapeutic options and different clinical scenarios after hemorrhagic stroke from intracranial aneurysm rupture, the often raised “clip or coil” debate does not cover the entire field of management of acutely ruptured intracranial aneurysms.

Pharmacologically induced hypothermia for the treatment of stroke and TBI

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Stroke and traumatic brain injury (TBI) are leading cause of human death and disability across the globe. Unfortunately, there are very few effective therapies for stroke and TBI patients. Most previous and current experimental treatments have focused on affecting one signaling pathway, regulating an individual membrane protein/channel/receptor (e.g. NMDA receptor) or targeting one type of cell death mechanism (e.g. apoptosis). The failure of many clinical trials that have used these approaches in recent years has generated the consensus that for a therapy to be effective against complicated CNS disorders such as cerebral ischemia and TBI, it requires overwhelming protective effects on multiple pathways and multiple cell types. So far, there has been no therapy that is truly multifaceted and clinically feasible for acute stroke/TBI patients. One potential therapy, however, stands out for its versatile protective effects on the brain, heart and other organs: Hypothermia therapy. Mild-to-moderate hypothermia has shown remarkable neuroprotective effects (up to 90% infarct reduction) against brain ischemia in animal and human studies. Some of the drawbacks to available cooling techniques of physical means are that they are slow (≥3 hrs) and not practical, which have hampered clinical applications of hypothermia therapy. Thus, chemical compounds that can be utilized for hypothermia therapy have long been sought after for clinical treatments. Using drug-induced hypothermia, it is expected that even a small drop in body temperature (1-2°C) is beneficial for preventing the detrimental post-injury hyperthermia, delay the evolution of the secondary injury, and thereafter extend the therapeutic window for other interventions. We have developed novel neureotensin derivatives such as ABS201, ABS601, and ABS363 that can pass through the blood-brain barrier to induce “regulated hypothermia”, reducing body and brain temperature by 3-5°C in around 30 min without causing shivering. Systemic studies, blood tests, and autopsy examinations showed no toxic or adverse effects of these compounds. Post-ischemic administration of these compounds markedly attenuates ischemia-induced neuronal cell death, blood-brain barrier damage and improved functional recovery. In a hemorrhagic stroke model of the mouse, ABS201 administration 24 hrs after the onset of stroke still showed significant neuroprotection and functional benefits. Our recent investigation also showed protective effects of drug-induced hypothermia against TBI. These compounds thus provide a novel therapy that takes full advantage of therapeutic hypothermia but with no obvious side effects. It is expected that drug-induced hypothermia can be developed as a new category of global brain protection drugs and help to translate the chemical/pharmacological hypothermic therapy into clinical applications.