Temperature Modulation for Neuroprotection after Acute Brain Injury

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A growing body of basic science as well as translational and human experimental data supports the concept that mild therapeutic hypothermia (TH) and therapeutic normothermia (TN) are beneficial for patients with acute neurologic injuries. At the cellular level, acute brain injury is characterized by an initial insult that is complicated by secondary biochemical and hemodynamic injuries. Events over hours to days lead to very different outcomes; injured cells may lyse, causing inflammation, releasing cytotoxic neurotransmitters, and perpetuating a cycle of injury. They may undergo apoptosis, or they may recover and return gradually to normal cellular function and activity. Aggressive clinical management during the early phases of injury can have a major impact on long-term neurologic outcomes.

Pathophysiologic Response
The variable vulnerability of different regions of the brain to ischemia depends on intrinsic metabolic activity of specific subpopulations of neurons, the type and mechanism of injury, and anatomic differences in blood supply. In the setting of circulatory arrest, the medial temporal lobes, the caudate and putamen, and the Purkinje cells of the cerebellum are the first regions damaged. In low-flow states, neurons in a watershed distribution between large-vessel vascular territories are more likely to be injured. When ischemia is caused by the combination of high intracranial pressure (ICP) and low cerebral perfusion pressure, such as in global cerebral edema, an isolated pattern of cortical laminar necrosis may develop. Finally, in traumatic brain injury (TBI), rotational points in the basal ganglia, midbrain and brainstem may develop ischemia and infarction due to disruption of the blood supply. Prolonged hypoperfusion due to any of these mechanisms may cause microvascular thrombosis, resulting in the “no-reflow” phenomenon and regional cellular necrosis, even if large vessel patency is restored.

Brain temperature has direct effects on the speed of enzymatic reactions and cellular metabolism, and it is an important modulator of brain injury. Hypothermia reduces the metabolic demands (and therefore ischemia risk) of the injured brain, decreases cytotoxic neurotransmitter release and inflammation, and decreases ICP without affecting systemic blood pressure. This reduces secondary injury by multiple pathways. Hypothermia also prevents the activation of apoptotic signaling pathways and stabilizes neuronal cell membranes. Conversely, fever activates inflammatory pathways, increases cellular metabolism, and is associated with more severe histological features of injury and worse long-term neurologic outcomes.

Uses for Temperature Management
While moderate and deep hypothermia (below 32°C) are associated with electrolyte disturbances, cardiac electrical instability, coagulopathy, sepsis and circulatory collapse, mild TH (≥32°C) generally is tolerated well. Aside from asymptomatic bradycardia, TH is associated with a low incidence of bleeding, hypokalemia, hemodynamically significant arrhythmias and infection.1,2 Development of pneumonia in mechanically ventilated patients with brain injury is common, and many clinicians offer preemptive antimicrobial prophylaxis.3 Hypothermia is immunosuppressive, and the incidence of infectious complications rises steeply after two to three days of therapy. Similarly, shivering increases systemic and cerebral metabolic demands, and aggressive suppression of shivering may prevent exacerbation of ischemic brain injury.4

Hypoxic-ischemic encephalopathy after cardiac arrest. Two randomized controlled trials confirm that 12 to 24 hours of TH at 32 to 34°C in encephalopathic adult survivors of cardiac arrest reduces mortality by 14%; one poor neurologic outcome is prevented for every six patients treated.1,5,6 Postimplementation reports have demonstrated that hypothermia can be initiated outside of the clinical trial environment with similar results.7,8

Additional indications for TH after cardiac arrest remain controversial. Many clinicians treat hypoxic-ischemic encephalopathy due to pulseless electrical activity, asystole, hypoxemia or asphyxia, and in-hospital cardiac arrests. Although these patients suffer similar mechanisms of neuronal injury, fewer than 10% have traditionally attained good neurologic outcomes. Some clinicians worry that aggressive treatment of these patients may only increase the
number of patients surviving with severe neurologic disabilities. It is our practice to perform TH on all encephalopathic cardiac arrest survivors unless severe shock is present or severe medical comorbidities exist.

Neonatal post-anoxic encephalopathy. A meta-analysis of four randomized trials supports the routine administration of mild TH for newborns with asphyxial hypoxic-ischemic encephalopathy, also showing that one poor neurologic outcome or death is prevented for every six infants treated. A randomized controlled trial involving 239 infants demonstrated improvements in mortality and neurologic outcomes at 18 to 22 months when systemic hypothermia was maintained at 33.5°C for 72 hours, followed by slow rewarming.

**Hepatic encephalopathy.** Studies conducted with small series of patients have concluded that TH effectively reduces ammonia levels, cerebral blood flow, refractory elevated ICP, cerebrospinal fluid lactate levels and vasopressor requirements in patients with advanced hepatic encephalopathy and cerebral edema. TH preserves cerebral autoregulation in hepatic failure, possibly by decreasing inflammatory cytokines such as tumor necrosis factor-α. Although promising, multicenter randomized data are lacking, and the risk of sepsis is high. Recent guidelines for the management of acute hepatic failure, developed by the U.S. Acute Liver Failure Study Group, suggest aggressive treatment of fever or shivering and recommend considering mild hypothermia (typically 33 to 35°C) when elevated ICP is refractory to standard medical management.

**Traumatic Brain Injury.** Although the largest randomized controlled trial of routine application of TH after TBI showed no mortality advantage, extensive experimental and clinical data suggest possible neuroprotective benefit. Meta-analyses also have suggested benefit and identified study design issues that may have confounded previous studies. A Brain Trauma Foundation meta-analysis of eight high-quality trials of prophylactic TH after severe TBI found an overall improved long-term Glasgow Outcomes Score in patients treated with TH and stronger benefit when TH was administered for longer than 48 hours. That group issued a “level III recommendation for optional and cautious use of hypothermia for adults with TBI.”

**Ischemic Stroke.** Basic science research supports the utilization of TH as neuroprotective therapy after acute ischemic stroke, and small series of studies have established its safety and feasibility. The performance of randomized controlled trials in ischemic stroke has been hampered by technical concerns such as shivering management, inefficient cooling devices, and difficulties with patient selection and enrollment. The increasing availability of neurologic intensive care units (ICUs) and improved cooling technologies will facilitate human research in temperature management for ischemic stroke.

**Therapeutic Normothermia after Brain Injury.** Distinct from efforts to reduce body temperature, interventions to maintain normal body temperature and avoid fever are associated with different challenges, and the benefit is yet to be proven. Fever is linked to increased mortality, functional disability and cognitive impairment in subarachnoid hemorrhage, 18 with increased morbidity and mortality in ischemic stroke and longer stay in the ICU. Fever also is associated with elevated ICP, lower Glasgow Coma Scale scores, and poorer functional status in TBI. Fever is an independent risk factor for longer ICU and hospital lengths of stay, mortality, and worse outcome in a general neurologic ICU population. Based on animal studies, the association between fever and worse outcomes may be causative, rather than a marker of disease severity. No randomized trial of TN has been published to support the routine use of aggressive fever control in patients with brain injury, but fever management is a standard practice in most neurologic ICUs.

**Conclusion**
Therapeutic temperature management increasingly is recognized as an important and practical component of the intensive care management of patients with acute brain injury. We anticipate clarification of the indications and exclusion criteria for TH and TN, with the development of subgroup applications in TBI, hepatic encephalopathy, and ischemic and hemorrhagic stroke. Large, multicenter trials of temperature management strategies for acute brain injuries are warranted, needed and worthy of increased attention and funding at the federal level.

**References**


Disclosures

* Author has no disclosures to report