

SYSTEMIC COOLING TO TREAT STATUS EPILEPTICUS: AN OLD IDEA BECOMES A HOT TOPIC

Hypothermia for Refractory Status Epilepticus. Corry JJ, Dhar R, Murphy T, Diringner MN. *Neurocrit Care* 2008;9(2): 189–197. **INTRODUCTION:** Status epilepticus (SE) can be refractory to conventional anticonvulsants, requiring anesthetic doses of medications to suppress seizures. This approach carries significant morbidity, is associated with a high fatality rate, and may not always control SE. Hypothermia has been shown to suppress epileptiform activity experimentally, but has not previously been used as a primary modality to control SE in humans. **METHODS:** Four patients with SE refractory to benzodiazepine and/or barbiturate infusions were treated with hypothermia (target temperature: 31–35°C) using an endovascular cooling system. All received continuous EEG monitoring, three were on midazolam infusions and one had recurrent seizures on weaning from pentobarbital. **RESULTS:** Therapeutic hypothermia was successful in aborting seizure activity in all four patients, allowing midazolam infusions to be discontinued; three achieved a burst-suppression pattern on EEG. After controlled rewarming, two patients remained seizure-free, and all four demonstrated a marked reduction in seizure frequency. Adverse events included shivering, coagulopathy without bleeding, and venous thromboembolism. Two death occurred, neither directly related to hypothermia; however, immunosuppression related to the use of barbiturates and hypothermia may have contributed to an episode of fatal sepsis in one patient. **CONCLUSIONS:** Hypothermia was able to suppress seizure activity in patients with SE refractory to traditional therapies with minimal morbidity. It appears promising as an alternative or an adjunct to anesthetic doses of other agents, but requires further study to better evaluate its safety and efficacy.

COMMENTARY

When status epilepticus (SE) is refractory to conventional antiepileptic medications, it is typically treated with anesthetic doses of barbiturates, benzodiazepines, or propofol. Even if these treatments end the SE, there is, nonetheless, significant associated morbidity and mortality. Better treatments, with fewer adverse effects, are needed to stop the seizures and reduce the risk of long-term neurological consequences from this condition.

In recent years, induced reduction of body temperature in the intensive care unit has become a common therapy for coma associated with cerebral injury. Mild (32–34°C) systemic hypothermia has been shown in randomized clinical trials to improve neurological outcome after cardiac arrest (1,2). It has become a recommended treatment for out-of-hospital cardiac arrest after ventricular fibrillation, and there also is evidence of its possible value following cardiac arrest that is associated with other abnormal heart rhythms or that occurs in the hospital (3). In addition, mild hypothermia has been applied to the treatment of patients with traumatic brain injury and increased intracranial pressure, with benefit in some circumstances (4). There is extensive evidence that cooling reduces synaptic transmission

in the brain, and recent work suggests that a key mechanism for this change may be the reduction of transmitter release from presynaptic vesicles (5). All of these results raise the question of whether hypothermia also might be an effective intervention for refractory SE.

This question has been addressed in a variety of experimental seizures. A body temperature of 28°C in rats reduces ictal discharges and prevents hippocampal neuronal loss from kainate-induced SE (6), and a temperature of 32.5°C decreases the widespread neuronal loss seen in SE induced by inhaled flurothyl (7). Focal cooling of the hippocampus to 23 to 26°C decreases seizure severity and afterdischarge duration during hippocampal kindling in the rat (8). These studies provide strong evidence for antiepileptic and neuroprotective effects in animals.

In humans, hypothermia has been long known to suppress epileptiform discharges (9), and moderate (30–31°C) body temperature reduction previously has been used in combination with thiopental coma to control refractory SE (10). However, the current study by Corry and coworkers is the first to use hypothermia as a therapy for refractory SE in humans without simultaneous barbiturate infusion. The four patients in this study did not have preexisting epilepsy, but presented with severe generalized SE that was refractory to several conventional antiepileptic medications and infusions of pentobarbital, phenobarbital, or midazolam. Each patient's temperature was

reduced to a range of 31 to 35°C by circulating cooled saline through balloons on the surface of an inferior vena cava catheter introduced through the femoral vein. The temperature was lowered until the seizures stopped on EEG monitoring; then, midazolam and vasopressor infusions were reduced or weaned entirely. Typically, the cooling period lasted 24 hours, and the infrequent seizures that occurred after warming did not require repeat cooling. A significant adverse effect was deep vein thrombophlebitis in three of the patients. The two surviving patients are seizure-free, and one is described as having no observable neurological deficits.

This study suggests that mild systemic hypothermia is a practical and effective method to treat refractory SE. Does this mean that this method is ready to be widely introduced into clinical practice? Not yet! Several key questions remain to be answered:

- What is the optimal cooling technique? Would an external cooling blanket be an effective alternative to the endovascular approach and have a lower risk of thrombophlebitis? In treating SE, speed is essential. Would an initial intravenous infusion of iced saline achieve more rapid cooling and improve efficacy? The current study appears to show that mild cooling is usually sufficient for seizure control; however, this finding needs to be verified in a larger series.
 - Does systemic hypothermia result in improved outcomes relative to other treatment options? The four patients in the current study had prolonged pharmacoresistant SE and, therefore, a rather unfavorable neurological prognosis. While it is noteworthy that cooling stopped seizures in all these patients, the overall outcomes for the group were not impressive. A better assessment of the neurological benefits of cooling could be made using hypothermia earlier in the SE treatment protocol, at the point when it has been demonstrated that the SE is refractory to bolus doses of conventional antiepileptic medications (e.g., lorazepam, phenytoin, phenobarbital, or levetiracetam) but before starting continuous intravenous infusions of benzodiazepines, barbiturates, or propofol. A subject group defined by these criteria would have a better overall prognosis than the patient cohort in the current study of Corry and coworkers, and modest improvements in outcomes might be easier to demonstrate.
 - Would systemic hypothermia be better tolerated and safer than the alternate pharmacological treatments? In addition to thromboembolism, adverse effects of concern with hypothermia include shivering, coagulopathy, pH changes, electrolyte disturbances, and immunosup-
- pression. An advantage of hypothermia appears to be a low risk of hypotension as compared with barbiturate infusion. The cooling method, body temperature, the duration of hypothermia, and comorbid conditions would be important factors influencing the occurrence of adverse effects.
- If cooling therapy ultimately were shown to reduce the neurological sequelae of SE, could it also reduce the risk of subsequent epilepsy? It is not uncommon for severe SE to result in chronic recurrent seizures in survivors. Prevention of neuronal loss may or may not result in an antiepileptogenic effect.

Only a randomized, controlled clinical trial could definitively determine whether systemic hypothermia has superior safety and outcomes relative to pharmacological treatment for SE that is not controlled with conventional antiepileptic medications. The work of Curry and coworkers demonstrates that such a trial is justified and would meet the condition of equipoise.

by John W. Miller, MD, PhD

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