Controlled normothermia in neurologic intensive care

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Preclinical and clinical studies of therapeutic hypothermia completed during the last 15 yrs have dramatically expanded our understanding of this treatment for a variety of neurologic diseases, especially traumatic brain injury (TBI), stroke, and cardiac arrest. With few exceptions, the preclinical studies have shown that cooling of the brain to 32–33°C after trauma or ischemia leads to reduced levels of excitotoxic amino acids, reduced inflammation, a reduction in the volume of tissue damaged, and improved functional outcomes. Recently, two clinical trials studied the use of this treatment for patients with cardiac arrest and found improved outcomes for those cooled to 32–33°C for 12 or 24 hrs after the arrest (1, 2).

However, the efficacy of hypothermia for patients with severe TBI is not as clear. Although small clinical trials completed during the 1990s found benefit for subgroups of TBI patients treated with hypothermia (3, 4), Clifton et al. (5) did not find any benefit in a large, multiple-center trial of 392 patients completed in 2001. The results of this trial were surprising given the strong preclinical evidence in support of the efficacy of hypothermia for TBI and given the results of the smaller, single-center studies. Clifton et al. (5) also found that hypothermia was effective in reducing intracranial pressure. However, elevated intracranial pressure is closely associated with poor outcomes, so the results of the study by Clifton et al. (5) raise confusion about the link between intracranial pressure and outcomes. Based on the results of this trial, Safar et al. (6) have raised serious questions about the ability to conduct multiple-center clinical trials sufficiently controlled to allow for meaningful results. A subsequent analysis (7) of the consistency with which patients were medically managed in the study by Clifton et al. (5) seems to confirm some of the suspicions of Safar et al (6).

It also is possible, however, that therapeutic hypothermia is not as important in preventing secondary injury as is the prevention of fever. In the study by Clifton et al. (5), the temperature in the normothermia patients was tightly controlled to 37–38°C, and fever was aggressively treated. Such close attention to the prevention of fever in the control group may have reduced the expected morbidity and mortality in that group, resulting in outcomes that were similar to the hypothermia group. Several retrospective studies of patients with stroke, spontaneous intracranial hemorrhage, and subarachnoid hemorrhage have found an association between fever and poor outcomes. In this article, I will review studies that describe potential deleterious effects of fever and the incidence of fever in a typical neurologic intensive care unit (ICU), and I will conclude with results of a clinical trial that used an invasive temperature-modulation device to prevent fever in the ICU.

Laboratory Evidence of the Effects of Fever

In animal models of ischemia and of percussive or contusive brain injury, brain temperatures of >39°C are associated with an increase in the extracellular levels of excitatory amino acids and free radicals and with more extensive breakdown of the blood–brain barrier, increased enzymatic inhibition of protein kinases, and worsened cytoskeletal proteolysis (8). In a rodent ischemia model, hyperthermia (39°C) superimposed on transient ischemia led to a ten-fold increase in ischemic neurons and a significant increase in calpain activation and spectrin degradation (9). Others have found that the deleterious effects of hyperthermia are not confined to the time immediately after the insult. In their rodent ischemia model, Baena et al. (10) showed that even at 24 hrs after the insult, brain temperatures of >39°C led to a significant increase in the number of ischemic neurons in selectively vulnerable brain regions.

Clinical Evidence of Adverse Effects of Fever

Several retrospective studies have found a significant association between fever and outcomes after intracerebral hemorrhage, subarachnoid hemorrhage, and stroke. In their study of 196 patients with spontaneous intracerebral hemorrhage, Schwarz et al. (11) found significantly worse outcomes for those who had rectal temperatures of >37.5°C than those who did not. Oliveira-Filho et al. (12) reviewed the outcomes of 92 patients with subarachnoid hemorrhage, and found that 38 of these patients had rectal temperatures of >38.3°C for ≥2 days during the first week after hemorrhage. The odds ratio for poor outcomes (death, vegetative survival, or severe disability) in the subgroup with fever was 1.4 (95% confidence interval, 1.1–1.88) when compared with the patients who had no fever. Several studies have shown a similar effect of fever on poor outcomes for patients with stroke (13–15). In a meta-analysis of those studies by Hajat et al. (16), fever after stroke was found to be associated with a significant increase in neurologic morbidity ($p < .0001$) and with a highly significant increase in death ($p < .000001$).

Fever in the Neurologic ICU

Those who treat critically ill patients with neurologic disease are well aware that fever is a common problem during

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the first several weeks after the insult. The most common cause is nosocomial infection, and endotracheal intubation is a well-known independent predictor of pneumonia. These patients usually require intravenous and intra-arterial catheterization for the administration of fluids and for continuous monitoring of blood pressure and central venous pressure, but such catheterization also increases the risk for infection and sepsis. Other causes of fever are atelectasis, particularly in postsurgical patients who are not intubated. Fever is a common side effect of phenytoin, an anticonvulsant frequently used for trauma patients and patients with intracranial hemorrhage. The presence of blood in the subarachnoid space also has been implicated as a central cause for fever.

In 1999, we reviewed the incidence of fever in the neurologic ICUs of our hospital (17). During a 12-month period, 428 patients were admitted with stroke (34%), severe TBI (32%), subarachnoid hemorrhage (13%), and a smaller proportion of other acute neurologic diseases. Rectal temperatures were routinely obtained and recorded every 2–4 hrs. For the purposes of this study, a febrile episode was defined as a rectal temperature of >38.5°C. In all cases, the nursing staff was directed to aggressively treat fever with acetaminophen and cooling blankets. Despite this directive, febrile episodes occurred in 46.7% of the patients. There was no apparent correlation with their admission diagnosis, but there was a significant correlation with length of stay in the ICU: febrile episodes were observed in only 15.5% of those who spent <24 hrs in the ICU but occurred in 92.6% of those who were in the ICU for ≥2 wks. Other studies have found an even higher incidence of fever for patients in the ICU, confirming a strong association with duration of ICU stay and with endotracheal intubation (18).

Correlation of Brain Temperature with Rectal and Bladder Temperature

Another concern, and one that is certainly magnified by the animal studies showing a strong association between secondary brain injury and elevated brain temperatures, is the observation that brain temperatures are usually higher than rectal or bladder temperatures after TBI. We compared brain, rectal, and bladder temperatures for 5 days in eight patients with severe TBI (19). Deep brain temperatures were measured using a microthermister attached to a ventriculostomy catheter. Simultaneous brain, bladder, and rectal temperatures were obtained each minute during that time, for a total of 30,000 measurements. At virtually all time points, the brain temperatures were higher than the rectal or bladder temperatures. Brain temperatures averaged 1°C higher than rectal temperatures, and in nearly 10% of measurements, brain temperatures were 2°C higher. The differences between brain and bladder temperatures were slightly less, on average, 0.8°C. However, differences were greatest when the rectal or bladder temperatures were elevated. Thus, patients with rectal temperatures of 38–39°C were very likely to have brain temperatures of 40–41°C. Rumana et al. (20) completed a similar study of brain and systemic temperatures in patients with severe TBI and found that brain temperatures were frequently 1.1°C higher then rectal temperatures. Jugular venous temperatures were measured and were found to correlate with core body temperatures, but not with brain temperatures. The greatest differences between brain and core body temperatures were observed when the cerebral perfusion pressure decreased to <50 mm Hg and the smallest differences when patients were treated with high-dose barbiturates for control of elevated intracranial pressure.

Can the Incidence of Fever in the ICU be Reduced?

During the last decade, several groups have developed invasive devices designed to more rapidly reduce body temperature or to better maintain normal temperature. Laboratory investigations have shown that direct cooling of the venous blood with heat-exchange devices inserted into the vena cava can more rapidly cool the patient, or better maintain normal temperature, than surface cooling techniques. In 2000, a multiple-center clinical trial was initiated by the Alsius Corporation to determine if a heat-exchange catheter it developed could significantly limit the incidence of fever in patients with several acute neurologic diseases. Twelve hospitals participated in the study and enrolled 296 patients. Adult patients with spontaneous intracerebral hemorrhage, subarachnoid hemorrhage, severe TBI, and severe cerebral infarction were studied. Patients were randomly assigned to a group of patients who had their body temperature regulated via a heat-exchange catheter placed into the superior vena cava or a group of patients who had conventional fever management using antipyretic medication and cooling blankets. The former group had the heat-exchange catheter placed into the superior vena cava by percutaneous insertion through the subclavian or internal jugular vein, and cooled saline was infused through two heat-exchange balloons attached near the distal end of the catheter. The temperature of the saline solution infused through the balloons was adjusted automatically according to feed back to the external pump/refrigerant device from a microthermister attached to a Foley bladder catheter. The device was set to maintain a body temperature of 37°C. In the control group, temperatures of >38°C were aggressively treated with a acetaminophen, ibuprofen, and cooling blankets as needed. The primary end point of the study was the time the bladder temperature was of >38°C, expressed as the "fever · time product," during a 72-hr interval beginning soon after admission to the ICU. At the completion of patient enrollment, the majority of patients had either subarachnoid hemorrhage or severe TBI as their primary diagnosis, and patients in both the control and experimental groups had a similar distribution of diseases. Likewise, the age, sex, race, weight, body mass index, Glasgow Coma Scale score, and National Institutes of Health Stroke Scale score were not significantly different between the two groups. Final analyses of the temperature data revealed that there was a 64% reduction in the fever burden for patients with the heat-exchange catheter compared with the control patients.($p < .0001$). Differences between the two groups were comparable among study sites and among presenting diseases. There also was a 61% reduction in the use of cooling blankets, 66% reduction in the use of other physical means of cooling, and 28% reduction in the use of antipyretic agents in the heat-exchange catheter group. There was no significant difference in the use of antibiotics or sedatives between the two groups. There was no increase in the incidence of infection, sepsis, deep venous thrombosis, or other medical complications attributable to the heat-exchange catheter. *Post hoc* analysis also revealed that the fever burden was significantly higher in patients who died

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(13.1°C hours) than in those who survived (7.7°C hours).

Summary

Preclinical studies of cerebral ischemia and trauma find increased brain tissue injury and worsened functional outcomes if the brain temperature exceeds 39°C. Several retrospective studies of patients with new-onset stroke, intracerebral hemorrhage, or subarachnoid hemorrhage support these observations. However, fever is very common among these patients early after the onset of their disease, particularly if they are in the ICU for a week or more, and brain temperatures are likely to be as much as 2°C higher than rectal temperatures. Finally, intravascular temperature modulation has been shown to be more effective for preventing fever than conventional methods, such as antipyretic medications or surface-cooling techniques. Further study is needed to establish if such better control of temperature will lead to improved outcomes.

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