Therapeutic Hypothermia

TBI *from page 1*

idence-based conclusions would support the following statements:

► Hypothermia improves outcomes.

► Hypothermia reduces elevated ICP.

► If the patient is cooled to greater than or equal to 32° C for no more than 48 hours, there are no clinically significant risks of infection, of cardiac arrhythmia, or coagulopathy."

He reported 10 of the 15 trials had at least 15 patients in each arm. Among these, he reviewed nine complete manuscripts (the exception being a study from China). That seven were single-center studies should not make them less highly regarded, according to Dr. Marion.

"In all seven there is a trend to improved outcomes, and most reach statistical significance. The only ones that don't show a trend to improved outcomes are the two multicenter trials," he said, questioning whether randomized multicenter trials are realistic for a condition as complex as traumatic brain injury (TBI).

Dr. Marion said that his analysis of cumulative outcomes from all nine studies found 52% of patients treated with hypothermia were alive and functional at designated times ranging from 3 months to 2 years afterward. Only 39% of those treated at normal temperatures did as well, he said. This 13% difference became 24% when the two multicenter trials were excluded.

He also described a published meta-analysis of hypothermia trials as flawed (Arch. Neurol. 2002;59:1077-83). It only gave weight to four trials, one of which had twice as many patients as the other three trials combined, he said. A second negative study (Ann. Surg. 1997;226:439-47) included few TBI patients and did not consider functional outcomes as distinct from mortality, Dr. Marion said.

A second presenter on clinical use of hypothermia, Stefan Schwab, M.D., of the University of Heidelberg (Germany) reported that his institution has cooled about 200 stroke patients. He characterized hypothermia as a promising neuroprotective therapy with the potential to control fever but said the evidence does not support making it a standard of care for ischemic stroke.

Among the many open questions still to be resolved, Dr. Schwab listed optimal time to target temperature, duration of cooling, target temperature, ventilation mode, and methods of cooling and rewarming. He also cited safety, efficacy, and whether it should be used in patients with moderate, severe, or very severe stroke.

"For optimal treatment of severe stroke, decompressive surgery is still the standard," Dr. Schwab concluded, speculating that hypothermia might be beneficial as an added therapy or in stroke cases that are severe but not very severe.

"Obviously hypothermia is something that works, but we need to see how we can use it," he said.

Michael A. DeGeorgia, M.D., of the Cleveland Clinic Foundation reviewed studies that led to the International Liaison Committee on Resuscitation (ILCOR) task force advisory statement endorsing use of therapeutic hypothermia after cardiac arrest (Circulation 2003;108:118-21).

"We're further ahead in head trauma and cardiac arrest. Maybe this is something we should be doing in selective patients," he said, suggesting that determination of which patients would benefit from hypothermia is another key question to be resolved.

"Hypothermia improves outcome in the right patient at the right time at the right temperature for the right duration when delivered safely. It's complicated. You have to be careful," he said. ■

CT Scan Preferred for Diagnosing Brain and Spinal Cord Injuries

PHOENIX, ARIZ. — Magnetic resonance imaging provides more detail about traumatic brain and spinal cord injuries but computerized tomography is much faster, according to a colonel in the U.S. Army Medical Corps who served in Afghanistan.

In head traumas, MRI is superior for all pathologies except skull fracture and acute subarachnoid hemorrhage, Geoffrey S.F. Ling, M.D., said at a meeting sponsored by the Society of Critical Care Medicine. It can give far more information about edema, diffuse axonal injury, contusions, hematomas, and posterior fossa lesions, but these can all be diagnosed more quickly with CT scans, he said; rarely does information gathered with an MRI change clinical management of the patient.

Consequently, Dr. Ling, director of the division of critical care medicine at the Uniformed Services University of the Health Sciences in Bethesda, Md., said he reserves use of MRI to establish a diagnosis in a patient who is not improving after several days in an intensive care unit and to establish a prognosis.

Dr. Ling recommended CT scans for all patients at high risk for intracranial pathology. These would include patients with focal neural signs, penetrating wounds, depressed skull fractures that are palpable, and impaired motor skills in the absence of alcohol or drugs.

CT scans should also be considered in moderate-risk cases: patients with a history of changed mental status, amnesia, progressive headache, serious facial injury, vomiting, evidence of a skull fracture, multiple traumas, possible child abuse, and age younger than 2 years.

"If the patient was knocked out for more than 5 minutes, I would go ahead and do a CT scan," he said. Plain x-rays should be used only in cervical spine injuries such as whiplash, for which they can diagnose tiny fractures, according to Dr. Ling. "The only time I will use plain films is for the neck," he said.

—Jane Salodof MacNeil

Multicenter Trials: Not Suited to TBI Research?

The clinical value of therapeutic hypothermia may not be measurable in large, randomized studies.

BY JANE SALODOF MACNEIL
Contributing Writer

SCOTTSDALE, ARIZ. — The validity of large, randomized multicenter clinical trials to evaluate treatments for traumatic brain injury was called into question by numerous speakers during the annual meeting of the Neurocritical Care Society.

Speaking on therapeutic hypothermia, Donald Marion, M.D., refused to condemn the treatment when its promise in small single-hospital studies was not borne out in a large, randomized, multicenter trial, the findings of which showed the regimen was no better than current therapies.

An estimated 15-20 drugs, including tirilazad mesylate, have failed to show effectiveness in multicenter trials of traumatic brain injury.

Dr. Marion, a neurosurgeon and senior research fellow at the Brain Trauma Foundation, New York, took aim at the process. "Are valid multicenter clinical trials for severe traumatic brain injury possible?" he asked in a leadoff presentation, which became the talk of a 3-day meeting "I really think there is something about phase III trials that impact the outcomes independent of the treatment you are trying to use."

Large, randomized, multicenter trials might be unsuited to the realities of neurocritical care for head trauma, according to Dr. Marion. The cases are too complicated "with multiple physiological variables that can affect outcome and, unfortunately, multiple critical care physicians making treatment decisions," he said, adding that patients with traumatic brain injury often have other severe injuries that further complicate their randomization.

Dr. Marion estimated that 15-20 drugs, including tirilazad mesylate, have failed multicenter trials in traumatic brain injury.

These physicians have strong individual biases that make complying with uniform protocols difficult, especially if the investigators are working at many different centers, he continued. Consistency within a center may make single-center studies a better measure of new treatments for head trauma, he suggested.

"My bias is very strongly that there is a lot of noise in multicenter trials that may have drowned out the potential benefit of a lot of therapies in the past," he said.

As chair of the hypothermia session, Michael N. Diringer, M.D., of Washington University, St. Louis, expressed surprise: "This is the first time I've heard someone argue we might want to think twice about how we interpret the results from multicenter trials," he said. "The ability to perform trials on very sick, very complicated patients across centers—to get everybody to do the same thing—is an enormous and maybe potentially impossible task."

Stefan Schwab, M.D., also complained of inconsistent protocols as a major problem in his talk on therapeutic hypothermia for stroke. However, he disagreed with Dr. Marion's position. Studies have used different temperatures, times to cooling, duration of cooling, etc., according to Dr. Schwab of the University of Heidelberg in Germany. What is needed, he said, is one large, randomized, multicenter trial with agreed-upon protocols.

"In my view, just randomized trials can show whether there is significance," he said, arguing that small studies can be too selective. "Pick one right patient in one center and one right patient in another center and you come up with 20 right patients overall," he said. "We want to treat patients with stroke with hypothermia all over the world."

Raj K. Narayan, M.D., of the University of Cincinnati, argued that therapeutic hypothermia should not be a standard therapy, so long as it passes muster only in small studies. "Large randomized trials have some limitations, and certainly small trials have limitations. Just so long as we are all aware what those limitations are, large randomized trials are, in general, one of the strongest ways of figuring things out," he said.

For Maxwell S. Damian, M.D., of the University of Leicester, England, the issues raised by Dr. Marion are a concern as his group advances beyond its single-center study of hypothermia in combination with coenzyme Q10 for head trauma. "That actually has been influencing our multicenter trial," he said. "We are restricting it to people we know personally who have a similar regimen of hypothermia. It's a big problem—method."

Another researcher, Michael F. Stiefel, M.D., of the University of Pennsylvania, Philadelphia, ruled out randomized trials in his group's work on brain tissue oxygen monitoring. He said it is now standard at his hospital based on data from a single-center study presented at the meeting.

"A lot of what we do in neurosurgery has never been randomized. We use something, and we see if it works. That's what we do. We wouldn't feel comfortable randomizing now." he said. ■