

Dire TBI Outcome Data Reflect Poor Methods

BY BETSY BATES
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HONOLULU — Disappointing clinical trial results should not suggest that outcomes cannot be improved in traumatic brain injury, only that study methodologies may need to be refined, Dr. D. James Cooper said during a plenary address at the annual congress of the Society of Critical Care Medicine.

To be sure, various interventions have had hopeful improvements in animal models, but not in human trials.

But the heterogeneity of the traumatic brain injury (TBI) population and “huge differences” in the specific trauma suffered may make study results look unfairly pessimistic, said Dr. Cooper, deputy director of the intensive care unit at Alfred Hospital, Melbourne.

Experimental treatments may be initiated too late because of logistical and informed-consent dilemmas, and older patients may be so unlikely to benefit that they skew results. And follow-up assessment periods may be too brief, because it appears that Glasgow Outcome Scale scores improve greatly over time, but very slowly, he said.

A number of lessons have indeed been learned, even from negative clinical trials, and several promising approaches are currently under review.

Serious doubt has been cast on the efficacy of early high-dose steroids, for example, following the curtailment

of the 10,000-patient randomized controlled MRC-CRASH (Corticosteroid Randomisation After Significant Head Injury) trial in the United Kingdom after excess deaths were reported in the steroid arm.

“It seems clear from the study that the use of an agent that has been very widely used, particularly in the developing world, clearly and unambiguously increases mortality, accounting for an absolute number of 3% excess deaths. I think it’s abundantly clear...[that the] use of high-dose steroids should cease,” said Dr. Cooper, associate director for Australia’s National Trauma Research Institute.

Because they lower vasopressor requirements in TBI patients, lower-dose steroids are used commonly in the intensive care environment, he noted. “There are no randomized controlled trials at all in this area, and it’s clear to me, [based on the MRC-CRASH results,] there needs to be... a reevaluation” of this practice, said Dr. Cooper.

Another unexpected finding stemmed from the Australian SAFE-TBI (Saline Versus Albumin Fluid Evaluation-Traumatic Brain Injury) study, in which Dr. Cooper participated. That study of nearly 500 patients confirmed that albumin is independently tied to mortality in TBI patients when it is used for intravascular fluid resuscitation in the first 28 days. In contrast, saline was associated with lower mortality and better neurologic outcomes in patients with moderate to severe TBI.

The reasons remain unclear, although Dr. Cooper hy-

pothesized that albumin may increase brain edema, prompting the use of other agents that could contribute to mortality; that it may increase bleeding or cause more coagulopathy; or that it may be the result of hemodilution.

The possibility remains that albumin’s negative effect on survival may be a class effect of colloids, he said.

A recent analysis of data from both the SAFE-TBI study and the earlier ATBIS (Australasian Traumatic Brain Injury Study) “[adds] to our strong feeling that saline alone might be worthwhile,” he said.

As a final note, Dr. Cooper outlined two ongoing international clinical trials of early decompressive craniectomy to reduce intracranial pressure.

The absolute risk of mortality was halved with early decompressive craniectomy versus medical therapy alone in a recent, 38-patient French study; but the trial was concluded early because of slow recruitment.

Dr. Cooper’s DECRA (Early Decompression Craniectomy in Patients With Severe Traumatic Brain Injury) trial at 21 sites is enrolling only patients younger than 60 years with blunt diffuse brain injuries—strict criteria that may be more conducive to interpreting results, he said.

So far, 112 patients have been enrolled of 165 anticipated, already more than the largest study ever conducted of early decompressive craniectomy, Dr. Cooper noted.

Among the first 42 patients who received surgery, the complication rate has been less than 10%, he said. ■

IMAGE OF THE MONTH

Susceptibility-weighted imaging (SWI) is a T_2^* MRI technique that takes advantage of both magnitude and phase to enhance contrast. The signal changes result from disturbances in a homogeneous magnetic field caused by paramagnetic, ferromagnetic, or diamagnetic substances, said E. Mark Haacke, Ph.D., professor of radiology at Wayne State University, Detroit, and director of the Magnetic Resonance Imaging Institute for Biomedical Research in Detroit.

Application of a magnetic field to the brain generates an induced field that depends on the applied magnetic field and the magnetic susceptibility of molecules within the brain. Signal intensity changes are dependent on several factors, including hematocrit, deoxyhemoglobin concentration, and the presence of hemosiderin and other paramagnetic or diamagnetic substances. The technique is very sensitive in detecting intravascular venous deoxygenated blood and extravascular blood products. Most blood products are paramagnetic (deoxyhemoglobin, intracellular methemoglobin, and hemosiderin), letting SWI take advantage of magnetic susceptibility effects.

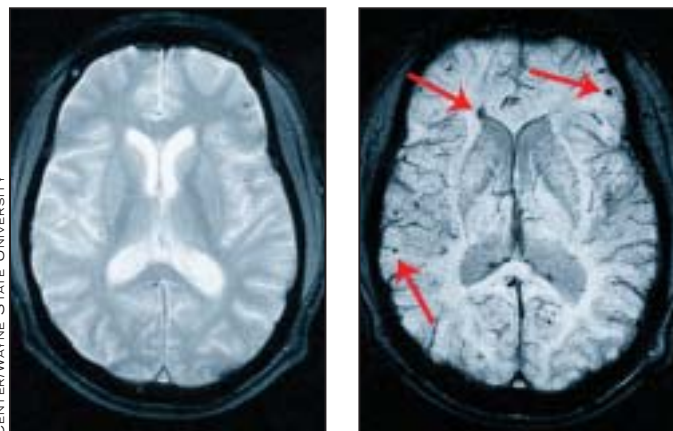
In brain trauma, the identification of smaller hemorrhages and their locations provides useful data about the mechanism of injury and potential clinical outcome. In this case, SWI showed several bleeds, including shearing of the confluence of the medullary veins into the septal vein. The bleeds appear as black areas, visible because of the iron in hemosiderin, which accumulated postbleeding.

The join between veins and venules tends to be an area of weakness susceptible to bleeding in brain trauma. In fact, for this patient, “almost all of these bleeds were on the venous side,” said Dr. Haacke. “It’s well known biomechanically that the veins are weaker than the arteries, but usually you end up seeing tearing and shearing of both arteries and veins when you have bad trauma.” One of the veins running to the front of the brain—to nerve-containing tissue—also seems to have bled, which could account for this man’s headaches.

Iron deposited from bleeding tends to stay in the brain. “Odds are that if we imaged 5 years later, we’d probably still see the major bleeding,” said Dr. Haacke.

The long-term goal is to correlate the imaging with motor and cognitive effects of trauma. “If you could eventually come up with a treatment that helped resolve some of the bleeding, for example, then you would potentially be able to watch and see with MRI if the person is getting better,” said Dr. Haacke.

—Kerri Wachter



Conventional MRI (left) hints at a possible bleed in the left front brain. SWI (right) reveals several bleeds from trauma.

Two New Studies Aim to Reduce Infant Head Trauma

SAN DIEGO — Two studies represent “an opportunity to do some useful intervention research in shaken baby syndrome or abusive head trauma,” Janet Saul, Ph.D., said at a conference sponsored by Rady Children’s Hospital, San Diego.

The first, led by Dr. Mark S. Dias, a pediatric neurosurgeon at Pennsylvania State University, Hershey, will test the efficacy of a hospital-based intervention. Components include a video and brochure about shaken baby syndrome, discussion about it with a clinician, posters, and a commitment statement for new parents to sign.

Parents receive four messages: crying is normal; there are ways to calm a baby; there are ways to calm yourself; it’s important to select other caregivers.

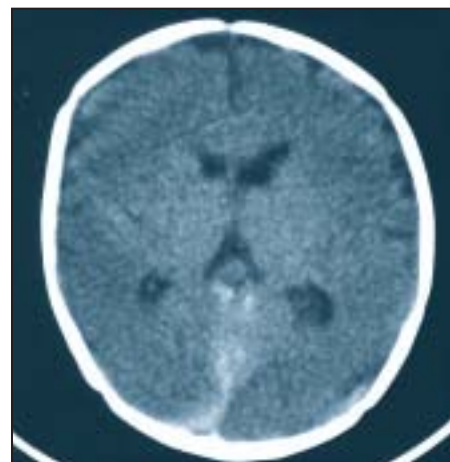
Also, half the counties in Central Pennsylvania will receive a “booster” session for parents who come to pediatric offices for 2-, 4-, and 6-month immunization visits.

In North Carolina, researchers led by Dr. Desmond Runyan of the department of

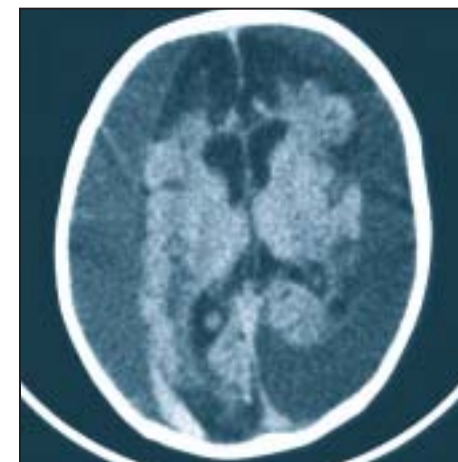
social medicine at the University of North Carolina at Chapel Hill are conducting a statewide preventive intervention that prepares parents to deal safely and explicitly with crying. Nurses in charge of nurseries in hospitals and birthing centers will show parents a DVD about the normalcy of crying and the ways to respond. The DVD will be given to parents to be shared with baby sitters and day care providers.

Pediatricians and family physicians also are being asked to deliver the same DVD and information to mothers at either prenatal care visits or the first postnatal visit. A mass media campaign to address infant crying and parent’s response to crying is also being developed by the National Center on Shaken Baby Syndrome, said Dr. Saul, a psychologist who is chief of the prevention development and evaluation branch in the division of violence prevention at the CDC’s National Center for Injury Prevention and Control, Atlanta.

—Doug Brunk



On the day of injury, a small subdural hemorrhage and subtle edema are seen.



Four weeks later, atrophy is seen, due to brain damage sustained by the injury.