Intracerebral Hemorrhage Guideline Update Issued

BY KATE JOHNSON
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Updated guidelines on the management of intracerebral hemorrhage reflect a wealth of new findings on diagnosing and treating the condition, according to Dr. Joseph Broderick, who chaired the guideline writing committee.

The guidelines, issued jointly by the American Heart Association (AHA) and the American Stroke Association (ASA) and published online, reflect "the recent dramatic increase in clinical trials of ICH/IVH [intracerebral hemorrhage/intraventricular hemorrhage]" whose initial findings "provide great hope for new and effective treatments," wrote Dr. Broderick, professor and chair of neurology at the University of Cincinnati, and colleagues (DOI: 10.1161/STROKEAHA.107.183689). The last AHA/ASA guidelines were issued in 1999. Since then, 15 pilot and larger randomized medical and surgical trials for ICH/IVH have been completed or are ongoing.

"I feel much better about where we are with intracerebral hemorrhage," Dr. Broderick said in an interview. "In general, the critical care of these patients is much improved . . . so I think we're making progress."

Probably one of the biggest changes in the new guidelines is that the role of surgery for ICH now is more limited than it was previously, said Dr. Broderick.

In addressing the feasibility and timing of surgical options, the guidelines relied heavily on the International Surgical Trial in Intracerebral Hemorrhage (STICH) (Lancet 2005; 365:387-97) and other smaller trials that suggested that surgery is not helpful in treating most supratentorial ICH and is probably harmful in coma patients.

However, "surgery—particularly craniotomy—may be helpful in treating those lobar clots within 1 cm of the surface that present in patients with milder deficits," wrote the authors. Additionally, surgical removal of cerebellar hemorrhages greater than 3 cm in size is recommended in patients "who are deteriorating neurologically or who have brain stem compression and/or hydrocephalus from ventricular obstruction." This is a class I recommendation, meaning "there is evidence for and/or general agreement that the procedure or treatment is useful and effective." Minimally invasive ways to remove clots are also under investigation.

In terms of medical management of ICH, the new guidelines suggest that recombinant activated factor VII (rFVIIa) is a potential new treatment. Administered within 4 hours of the ICH, rFVIIa may limit bleeding, reduce mortality, and improve patients' functional outcome at 90 days. However, the results of the rFVIIa in Acute Hemorrhagic Stroke Treatment (FAST) trial, presented last month at the American Academy of Neurology meeting in Boston, showed no reduction in the rates of mortality or severe disability with either of two doses of the drug, although it did reduce hematoma growth by up to 50% more than placebo.

"We have to rethink where and on whom we want to use this. What's important for right now is that use of factor VII should only be done in the context of a clinical trial," said Dr. Broderick.

He added that the trial investigators were disappointed not to have found the same clinical effect of rFVIIa that had been found in a previous phase II trial, "which was actually a very prominent effect, but now we know we have a medication that actually slows bleeding. … If you can stop the bleeding—and we know continued bleeding is related to [a] bad outcome—we have a chance to change the natural history of the disease. But we have to do that in the first several hours, likely."

Blood pressure management, although addressed with some suggestions in the guidelines, remains an open question awaiting the results of some ongoing clinical trials. "The primary rationale for lowering blood pressure is to avoid hemorrhagic expansion from potential sites of bleeding," wrote the authors. However, for primary ICH, "little prospective evidence exists to support a specific blood pressure threshold," they noted. "Until ongoing trials of blood pressure intervention for ICH are completed, physicians must manage blood pressure on the basis of the present incomplete evidence."

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DR. BRODERICK

Recommendations for imaging have changed from the previous guidelines. "Before, a CT scan was the primary option for evaluating stroke patients in an emergency," said Dr. Broderick. "Data now show that MR scans also do the job, and both are first-choice options," each carrying a class I recommendation. Specifically, "CT may be superior at demonstrating associated ventricular extension, whereas magnetic resonance imaging . . . is superior at detecting underlying structural lesions and delineating the amount of perihematomal edema and herniation," say the guidelines.

For the first time, the guidelines address end-of-life issues and withdrawal of care. "This is the first time the guidelines try to address how and when physicians should discuss 'do-not-resuscitate (DNR)' orders," said Dr. Broderick. DNR orders are often inappropriately associated with a lack of aggressive care in the first 24 hours following ICH, a trend the guidelines aim to change, he said. The class II (conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment) recommendation urges "careful consideration of aggressive full care" in the first 24 hours, and that new DNR orders during that time be postponed.

"ICH is an extraordinarily deadly disease. Forty percent or more of people are going to be dead in a month, and half of those deaths occur in the first couple of days." But one of the things we want to make certain doesn't happen is people saying 'it's a pretty big hemorrhage so we're just going to let the person go' without really seeing what they can do in the first 24-hour window." ■

Promise of rFVIIa Dimmed In Hemorrhagic Stroke Trial

BY MICHELE G. SULLIVAN
Mid-Atlantic Bureau

Boston — Despite high hopes for success, a phase III trial of the first medical therapy for intracerebral hemorrhage showed that the drug was no better than placebo in improving rates of death or disability 3 months after the bleed occurred.

Although recombinant activated factor VII (rFVIIa) reduced hematoma growth by up to 50% more than placebo, neither of the doses tested in the Recombinant Factor VII in Acute Intracerebral Hemorrhage Trial (FAST) improved rates of mortality or severe disability, Dr. Stephan Mayer said at the annual meeting of the American Academy of Neurology.

The results are an enormous disappointment to researchers and clinicians who felt that the drug's stellar phase IIB trial results showcased its potential to stop intracerebral bleeding and improve the dismal chances of patients who experience such an event. "In its phase IIB study, the drug created such a tremendous improvement that it almost seemed too good to be true," with those in the active groups 38% less likely to die than those taking placebo, Dr. Mayer said. "And in fact, in this larger phase III trial, we found out that it was."

The phase III FAST trial was conducted in 26 countries and randomized 841 patients to placebo or rFVIIa in doses of 20 or 80 mcg/kg. As in the earlier trial, patients had to receive the drugs no more than 4 hours after the onset of symptoms. The FAST demographics were fairly well matched, Dr. Mayer said, with two notable exceptions. There were significantly fewer intraventricular hemorrhages in the placebo group (29% vs. 35% in the 20-mcg and 41% in the 80-mcg groups). Left ventricular hypertrophy was also more prevalent in the treatment groups than in the placebo group, said Dr. Mayer, director of the neurologic intensive care unit at the Columbia-Presbyterian campus of the New York Presbyterian Hospital, and a principal investigator in the FAST study.

However, the mean time from symptom onset to treatment was identical in all groups (109 minutes), and almost all patients were treated within the 4-hour time frame (20% within 2 hours and 75% within 3 hours of symptom onset).

Safety was good, he said. The overall prevalence of thromboembolic events was no different among the groups (11% in placebo and the 20-mcg group, and 13% in the 80-mcg group). The frequency of venous thromboembolic events was similar (6% in placebo and 5% in each of the active groups), but arterial events were slightly more common in the 80-mcg group (10% vs. 6% in the 20-mcg group and 5% in the placebo group).

The increase in arterial events in the 80-mcg group was driven by a slight increase in myocardial ischemia and cerebral infarction during the first few days of dosing, Dr. Mayer said. "However, the total number of deaths among these patients was similar between groups, with two in the placebo group, four in the 20-mcg group, and five in the 80-mcg group."

Thromboembolic events occurred slightly sooner in the 80-mcg group as well, he said.

The drug successfully decreased bleeding by 24 hours in the active groups. The placebo group had a mean increase of 26% in hematoma volume, whereas the increase was 18% in the 20-mcg group and 11% in the 80-mcg group. The absolute increase in hematoma volume by 24 hours was 7.6 mL in the placebo group, 4.7 mL in the 20-mcg group, and 3.8 mL in the 80-mcg group. "In terms of bleeding we essentially replicated our findings from the earlier trial," Dr. Mayer said. "There was a highly statistically significant difference between placebo and the 80-mcg/kg group." The study also determined that patients treated earlier experienced greater reductions in hematoma volume growth than those treated later.

However, the changes in bleeding did not translate into any significant improvements in clinical outcome. At 3 months, mortality was 19% in the placebo group, 18% in the 20-mcg group, and 21% in the 80-mcg group.

The combined end point of death or severe disability (a score of 5 or 6 on the Modified Rankin Scale) was not different among groups (24% in the placebo group, 26% in the 20-mcg group, and 29% in the 80-mcg group). "Actually, the 80-mcg group had slightly, but not statistically significant, higher odds of having a bad outcome than the placebo group did," Dr. Mayer pointed out.

At the end of the trial, only 20% of the patients in each group were free from disability.

"In the first 2 weeks (of the phase III study), we did see greater mortality in the placebo group, but by the completion of the study, this effect was lost. The early deaths were directly tied to the neurologic event, including withdrawal of life support and brain death. After 15 days, the deaths we saw were more often related to comorbid illnesses, and they occurred mostly in our more elderly patients." ■