Timing Is Everything in Intracerebral Hemorrhage

To the Editor:

Hallevi and coworkers recently reported on the off-label use of rFVIIa in 46 patients with ICH.1 Twenty-four patients received rFVIIa within 3 hours, and 22 within 3 to 4 hours. Volume increase and outcome at discharge were compared with 148 historical controls. The authors did not find a difference in reduction of volume increase between the 0 to 3 and the 3 to 4 hour group. Nor did they find a difference in outcome between the factor VIIa treated and the control patients. They conclude that timing of hemostatic therapy may not have an influence on volume reduction or outcome in ICH patients.

We are not as quick to agree with this conclusion, for the following reasons: First, mean volumes were remarkably smaller—only one-third—than volumes that were found in FAST.2 Size of baseline volume plays an important role because it is a predictor of growth and outcome.3 Growth reductions may have a more important impact on outcome when baseline ICH volume is larger to begin with. Second, volume was measured with the ABC/2 method. This method was developed for assessing volume at bedside. Though the inter-rater agreement for hematoma volume was assessed as “excellent,” this method may still be imprecise. This may be important because, as we have recently shown, every milliliter counts when it comes to the relation of outcome and mortality.4 Third, edema volume was not assessed and IVH volume was only registered as absent or present. It is, however, known that both these variables may have an important impact on outcome. Thus, Gebel and coworkers found better outcomes with higher relative edema volumes.5 Several studies have shown that IVH volume is an independent predictor of poor outcome,6,7,8 and increases in IVH volume within 24 hours was another predictor of poor outcome.8 Hallevi and coworkers reported that 5.4% of the rFVIIa-treated patients had bleeding related to warfarin intake and another 9% had hematoma evacuation. These patients (14%) were removed from the efficacy analysis, which further reduces the already small number of patients, further questioning the meaningfulness of the conclusions.

Concerning safety, the authors report thrombotic events in 12.9% of rFVIIa-treated patients. In the discussion, they refer to the ongoing issue of safety of rFVIIa. It would have been interesting to know whether there were thrombotic events in the control group. This is particularly critical because the discussion about the relation of safety and outcome certainly needs a consideration of controls, given the large differences in outcome between the placebo groups of the Phase-II and the FAST trial.

Finally, with 24 and 22 patients in the 2 treatment groups, the power to say anything about timing of treatment and growth of ICH and outcome is extraordinarily limited—particularly when other baseline variables are strongly related to both outcome and hemorrhage growth and act as confounders. Direct comparisons between the 2 treatment groups on these other key variables would be highly unlikely to be significant without enormous differences, again because of the very small sample size.

We performed an analysis on data from FAST to identify a subgroup of patients who may benefit from treatment.9 This analysis demonstrated that, besides age and baseline volume of ICH and IVH, timing of treatment within 2.5 hours were prerequisite conditions for good clinical outcome with rFVIIa. We have also demonstrated that rFVIIa decreases hemorrhage growth in both the Phase-II and Phase-III FAST trials,2 and that growth of ICH decreases with increasing time from onset of ICH.3 Thus, there is a relationship between time-to-treatment with rFVIIa and its effect on growth of ICH. What has yet to be demonstrated in a Phase-III trial is that the decrease in hemorrhage growth is associated with improved long-term outcome, and here timing may play a key role.

Disclosures

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