An Age Old Question
Does Size Really Matter?

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See related article, pages 307–312.

The Intensive Blood Pressure Reduction In Acute Cerebral Hemorrhage Trial (INTERACT) trial suggests that early, intensive blood pressure (BP) lowering can attenuate hematoma extension or growth (HE) 24 hours after intracerebral hemorrhage (ICH). The primary goal of this more detailed analysis published in this issue of Stroke is to determine if the BP-lowering effects on HE observed at 24 hours were maintained at 72 hours. Maintaining such a therapeutic effect will be needed if long-term hematoma growth limitation is to have hope of producing a clinical benefit. The result of this secondary analysis is quite clear. Intensive BP lowering to 140 mm Hg systolic has a long-term effect on limiting growth of clot size; the overall difference of 2.81 mL of clot growth prevented over 72 hours was statistically significant (95% CI, 1.04 to 4.56; \( P = 0.002 \)). Despite this prevention of HE, there were no appreciable effects on perihematomal edema. The clinical value of limiting HE by 2.81 mL is unclear.

The INTERACT trial program has moved on to a Phase III trial, INTERACT 2, which tests for long-term functional benefits related to intensive BP lowering in the initial 6 hours after ICH presentation. This trial is very important because: (1) despite the adverse effect of volume growth on outcome, we have no treatment for HE; (2) preliminary evidence from INTERACT and Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) suggests that BP lowering can be performed safely and could have functional benefit; and (3) BP is markedly elevated in the initial phases of ICH, presenting an easy target for possible improvement in clinical management of ICH and ICH HE. Unfortunately, the HE reduction strategy has failed once. The pivotal activated factor VIIa trial, Factor seven for Acute hemorrhagic Stroke Trial (FAST), did not demonstrate improved functional outcome despite limiting HE by a mean of 3.8-mL reduction. This treatment effect is quite similar to the effect we see in the current INTERACT trial data. However, additional analysis of the INTERACT data presented in the current report gives us important new information about the type of change that may be needed to demonstrate long-term benefit. Table 3 divides the INTERACT subjects into groups based on the amount of enlargement that occurred (ie, in 2-mL increments of clot size enlargement). Inspection of this data reveals that the distribution of subjects with HE is skewed with the largest proportion of subjects' HEs being \( \geq 6 \) mL enlargement and only a small group having \( > 6 \) mL enlargement. Most interesting, however, is that the intensive treatment cohort has fewer enlargements of the largest type (ie, \( > 6 \) mL). Post hoc analyses are not always reproducible from trial to trial; however, this finding bears considerable further investigation because: (1) it is biologically plausible that a HE threshold for producing clinical effects exists; and (2) it is likely that clinically important functional impairments happen with large HEs, but not with small HEs. The INTERACT data presented in Table 3 allows us to ask several critical questions about HE in general for the first time: Were the effects on hematoma growth also skewed in the FAST and NovoSeven trials? Was there heterogeneity of these effects between treatment groups in those trials?

The crucial question that remains unanswered in all ICH trials is, does a volume or HE size threshold exist for benefit? For example, in BP trials (INTERACT 2), what size HE must be prevented for a subject to have real, long-term functional benefit? On the other hand, for surgical clot removal trials (Surgical Trial in Intracerebral Hemorrhage [STICH] II, Minimally Invasive Stereotactic Surgery rt-PA for ICH Evacuation [MISTIE], Combined Approach to Lysis Utilizing Eptifibatide and rt-PA in Acute Ischemic Stroke [CLEAR] III), what size minimum reduction is needed to see benefit in long-term functional outcome?

The data presented here suggest this size threshold could be \( \geq 6 \) mL. If the findings demonstrated here are reproducible, then we may have a useful volume threshold that can become a measurable clinical target for BP and surgical trials. For example, if we use the data in Table 3, then we need to design treatments to make a difference of \( \geq 6 \) mL. Also, we need to power our studies to test groups of patients with ICH large enough to expect a substantial number of subjects with \( \geq 6 \) mL HEs that might be remediated by BP-lowering therapies. Alternatively, we need to remove \( > 6 \) mL to consider surgical removal adequate. Also, we need to design surgical therapies so that this target volume can be removed predictably from the majority or from all subjects.

Our treatments must be as effective in altering people’s lives as they are statistically significant with respect to surrogate variables such as clot size. Validating a clinically meaningful clot size threshold could be the first step. Stay tuned for the answers. Like in the past, the answers may not be what we predict, but we are obliged to make sense of our results. Today, for the INTERACT trial data, size seems to matter.
Disclosures
None.

References


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