Blood Pressure in Intracerebral Hemorrhage — How Low Should We Go?

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Intracerebral hemorrhage is one of the most devastating forms of stroke. The median 1-month case fatality rate is 40%, and only 12 to 39% of patients achieve functional independence. Although previous trials of therapies for patients with this condition have not shown a benefit with respect to outcome, targeted blood-pressure management after an intracerebral hemorrhage has been both a promising and a contentious area of recent study. Early elevations of blood pressure are common after an intracerebral hemorrhage, and many have debated whether this response is adaptive (to maintain perfusion to an ischemic penumbra surrounding the hematoma) or potentially deleterious (resulting in rebleeding, peri-hematoma edema expansion, or both). Current American Heart Association guidelines suggest a target mean arterial pressure of less than 110 mm Hg or a blood pressure of less than 160/90 mm Hg, with some consideration given to maintaining a reasonable cerebral perfusion pressure in patients with suspected elevations of intracranial pressure. These guidelines, however, acknowledge that this blood-pressure target is arbitrary and not evidence-based. A lower-level recommendation was given for reducing blood pressure to a systolic target of 140 mm Hg. This recommendation was based, in part, on the promising pilot results of the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT), which showed a small, but significant, attenuation in hematoma growth over the course of 72 hours with aggressive lowering of blood pressure (systolic pressure of <140 mm Hg), without an increased risk of adverse events.

Anderson et al. now report in the Journal the eagerly anticipated results of the international phase 3 INTERACT2 trial. This trial provides the best data, to date, on acute, targeted blood-pressure control after spontaneous intracerebral hemorrhage. The primary end point (a score on the modified Rankin scale of 3 to 6, with a score of 0 indicating no symptoms, a score of 5 indicating severe disability, and a score of 6 indicating death) showed a trend toward significance (P=0.06). When the end point was examined from a different prespecified vantage point — an ordinal analysis of the modified Rankin score (which has inherently better power to show effect) — a significant improvement in the outcome was seen with intensive therapy. Interestingly, if a score on the modified Rankin scale of 2 to 6 had been selected as the primary end point, as is typical in many trials involving patients with an ischemic stroke, the results would have been significant with a lower point estimate (odds ratio, 0.83; 95% confidence interval, 0.70 to 0.98; P=0.03). In addition, significantly more patients in the intensive-treatment group than in the standard-therapy group had active treatment and care withdrawn (5.4% vs. 3.3%). It is possible that this discrepancy contributed to less significant differences in outcome between the intensive-treatment group and the standard-therapy group.

The reasons behind the trend toward improved outcomes remain a mystery, however. There were no significant absolute or relative changes in hematoma growth in the intensive-treatment group as compared with the standard-treatment group. Indeed, the volume differences between the groups was minute (adjusted mean volume, 1.4 ml). It remains a possibility that elevated blood pressure could have other systemic effects that affect the outcome. In addition, in patients...
with disturbed autoregulation, elevated blood pressure could lead to increased cerebral blood volume and consequently elevated intracranial pressure.

If the results of this study with respect to the primary outcome were not as robust as some may have hoped, practitioners should be reassured by the safety data presented in the trial. The authors found no significant differences between patients receiving intensive blood-pressure-lowering treatment and those receiving the standard treatment with respect to neurologic deterioration, expansion of the intracerebral hemorrhage, ischemic stroke, cardiovascular events, or severe symptomatic hypotension — findings that were consistent with the results of previous positron-emission tomographic neuroimaging studies, which failed to show an ischemic penumbra surrounding an intracerebral hematoma.8

Some limitations of this trial bear mentioning. First, more than two thirds of the participants were from China. Although the incidence of intracerebral hemorrhage in Asian populations is more than twice the incidence in other races, it is not clear that race or ethnicity has a major effect on outcome.9 Because more patients were enrolled in Asia, the most commonly used blood-pressure-lowering drug was an intravenous alpha-adrenergic antagonist, urapidil, that is not available in the United States. Though a drug effect seems unlikely, it remains a possibility that could limit the generalizability of the results. Second, 72% of the patients in this study had hypertension, and 84% had primarily deep hematomas that were of small volume (median, 11 ml). This could also limit the generalizability of the results. However, no significant differences in the primary outcome were seen on the basis of the region of enrollment or the volume or location of the hematoma. Third, no data on intracranial pressure or cerebral perfusion pressure were shown for either blood-pressure group. Though 62% of the patients in each group received mannitol, suggesting that they had increased intracranial pressure or radiologic evidence of edema, values for intracranial pressure were not reported. Patients with elevated intracranial pressure may require a higher mean arterial pressure to maintain target cerebral perfusion pressure. In such a population, multimodality monitoring may guide individualized blood-pressure goals.

The Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II trial9 is the ongoing North American complement to INTERACT2. This study also randomly assigns patients to a target systolic blood pressure of less than 140 mm Hg or less than 180 mm Hg but requires the use of nicardipine as the sole blood-pressure-lowering agent. It is hoped that this trial, which has similar primary and secondary end points and results due in 2016, will corroborate the results of INTERACT2. Nonetheless, given that INTERACT2 showed a trend toward a reduction in the primary outcome of death or severe disability, significant improvement in secondary functional outcomes, and reassuring safety data, acute blood-pressure reduction to a target systolic blood pressure of 140 mm Hg or less appears to be a reasonable option for patients with spontaneous intracerebral hemorrhage.

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