INTERACT-2
Should Blood Pressure Be Aggressively Lowered Acutely After Intracerebral Hemorrhage?

Michael D. Hill, MD, MSc, FRCPC; Keith W. Muir, MB, MD

Blood pressure (BP) lowering after spontaneous intracerebral hemorrhage (ICH) is intuitively attractive as a means to prevent continued bleeding or perihematomal edema. Concerns about potential reduction of cerebral perfusion pressure with concomitant risk of ischemia, particularly among patients with a recalibrated autoregulatory curve as a consequence of chronic hypertension, were largely mitigated by imaging studies that found no significant reduction of cerebral blood flow in the face of pharmacological BP lowering.\(^1\) and the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT) pilot study.\(^4\) The INTERACT investigators have now formally put the concept to test and have shown that if there is a clinical effect of BP lowering, it is fairly muted and smaller than anticipated.

Of 2794 patients with spontaneous ICH, the relative risk for poor outcome was 0.94 (0.87–1.002), \(P=0.063\), in the intensive BP-lowering group (to target systolic pressure \(\leq 140\) mm Hg) compared with the control guideline arms of the trial by 30 minutes after randomization, target systolic BP of \(\leq 140\) mm Hg. Various permutations of modified Rankin Scale dichotomization were also nonsignificant when adjusted for baseline factors. The Rankin shift analysis using ordinal logistic regression was marginally significant in favor of the intensive BP-lowering group (\(P=0.04\)).

Importantly, no differences in mortality and major safety events, including neurological worsening, were observed. As shown in Intracerebral Hemorrhage Acutely Decreasing Arterial Pressure Trial (ICH-ADAPT),\(^1\) perihematomal ischemia does not develop and, with the absence of any neurological complications with aggressive BP lowering in INTERACT-2,\(^5\) offers further assurance of the safety of acute BP treatment.

Hematoma expansion has been postulated to be the mechanism of worsening after acute ICH and the principal mechanism by which aggressive early BP lowering might act. In the pilot INTERACT, BP lowering was associated with attenuation of hematoma growth by a small margin.\(^6\) But in INTERACT-2,\(^5\) BP reduction was not associated with any change in hematoma volumes among the subgroup of patients who underwent repeated computed tomographic scanning at 24 hours. Possibly, this was because many of these hematomas were already stable; treatment occurred at a median of just 4 hours from onset, although subgroup analysis found no heterogeneity between those randomized <4 hours and \(\geq 4\) hours. Furthermore, the average hematoma volumes were small at 11 mL; small hematomas show the smallest relative growth, and so it is possible that many of these patients were not prone to progressive hematoma enlargement and clinical deterioration over hours.

The lack of a biological substrate for the mechanism of clinical deterioration may offer a clue to the interpretation of the study. A key issue is likely to be time. Much like the trials of recombinant factor VIIa,\(^7,8\) patients largely commenced treatment in the 3- to 4-hour time window, which may be too late to prevent hematoma expansion. BP lowering has the additional problem of rather gradual action; although there was \(\approx 10\) mm Hg difference in systolic BP between aggressive and routine guideline arms of the trial by 30 minutes after randomization, target systolic BP of \(140\) mm Hg was not achieved until 6 hours in the intensive group. Moving treatment into the prehospital arena will be required to truly test the hypothesis that early aggressive BP lowering might reduce hematoma expansion. Several small clinical trials are exploring this issue with oral, intravenous, or transdermal agents, and some limited data on outcomes in ICH will be forthcoming from the Field Administration of Stroke Therapy-Magnesium (FAST-MAG) trial.\(^9\)

The medical treatment of these patients was varied. Patients had combinations of urapidil, labetalol, nicardipine, nitrates, hydralazine, and diuretics. Use of mannitol in up to two thirds of patients in both groups is not clearly explained because median 24-hour hematoma volumes were only 20 mL, and raised intracranial pressure, therefore, is unlikely to be a concern. It remains possible that some of these medicines are actually harmful and that this confounded the BP-lowering effect in much the same way as antiepileptic drugs may reduce the efficiency of inpatient stroke rehabilitation. Small numbers of subjects treated with each individual agent and the common use of multiple agents make any attempts at subgroup analysis uninformative. More homogeneous data will be forthcoming.
eventually from the North American Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial in which intravenous nicardipine is the sole intervention.

Several minor factors might have contributed to the failure to meet the prespecified end point with a sample size that seemed adequate. Of the guideline BP-management group, 391 out of 1436 (27%) patients received intravenous antihypertensive treatment within 1 hour of randomization, whereas 278 out of 1403 (20%) patients assigned to intensive BP reduction did not, despite only a minority of these patients having achieved target BP, and indicating a probable higher rate of variation from the trial protocol than the 10% that was allowed for in the design. A significantly greater number of patients also had decisions to limit or withdraw active care in the intensive treatment arm (5.4% versus 3.3%), which suggests some systematic difference in non-trial aspects of medical care. Notwithstanding these potential confounders, the trial had adequate sample size to detect only a moderately large treatment effect (14% relative or 7% absolute reduction in poor outcome), and the neutral outcome indicates that this large an effect, at least, is unlikely to be achieved. INTERACT-2 might also be interpreted as the latest in a series of trials unlucky enough to have backed the wrong horse in choice of primary end point but which had a positive result on a secondary ordinal shift analysis. However, these results should really emphasize the importance of designing trials with a more conservative estimate of effect size than has been the habit in stroke, rather than calling for the assistance of novel statistical approaches to rescue the situation, and especially so where the intervention is unlikely to cause harm.

At this time, it seems to be safe to lower BP among patients with spontaneous ICH, including use of intensive treatments to achieve this rapidly. A target of 140 mmHg systolic is safe and reasonable. However, any benefit for treatment is smaller than anticipated and additional data are needed to recommend wholesale changes to routine clinical practice.

Disclosures

None.

References


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