Editorial

Optimal Blood Pressure After Intracerebral Hemorrhage
Still a Moving Target

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If you have been following the literature in recent years and feel confused about how to manage acute hypertension in patients with intracerebral hemorrhage (ICH), you are not alone. Two similar randomized controlled trials reaching seemingly different conclusions can confuse anybody.[1,2] However, as always, the devil is in the details. It is not just about the blood pressure (BP) target, but also about how and when you reach it.

The INTERACT-2 trial (The Second Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial) evaluated nearly 2800 patients with acute hypertension within 6 hours of ICH onset randomized to target systolic BP <140 or <180 mm Hg.[1] Hypertension could be treated with any drugs available, and patients were treated to remain below their BP target for 7 days. Death and moderate or severe disability at 90 days (modified Rankin score of 3–6) did not differ significant between the 2 arms (odds ratio, 0.87 with systolic BP <140 mm Hg; 95% confidence interval, 0.75–1.01; *P*=0.06), but functional outcomes were better in the intensive treatment arm on a prespecified ordinal shift analysis of the modified Rankin score. Serious adverse events were similar in the 2 groups. On the basis of these results, the AHA guidelines on management of ICH were modified to recommend treating acute hypertension to keep a systolic BP <140 mm Hg.[3]

Yet, ATACH-2 (Antihypertensive Treatment of Acute Cerebral Hemorrhage-II) was subsequently completed and moved us back to the drawing board. This trial randomized patients with acute ICH and hypertension to the same 2 systolic BP targets (ie, <140 or <180 mm Hg), but antihypertensive treatment had to be initiated within 4.5 hours of hematoma onset and intravenous nicardipine had to be used as first-line medication. The BP target was maintained for 24 hours.[2] After enrollment of 1000 patients (planned n=1280), the trial was terminated because of futility after a prespecified interim analysis demonstrated that the rates of death or severe disability (modified Rankin score of 4–6) at 90 days were similar in both arms (relative risk, 1.04 with systolic BP <140 mm Hg; 95% confidence interval, 0.85–1.27; *P*=0.72 on analysis adjusted for prognostic factors). Unlike INTERACT-2, ATACH-2 showed no difference in the ordinal distribution of modified Rankin scores and instead showed an increase in renal adverse events within 7 days on the intensive treatment arm, which could have been caused by excessive BP lowering on the first day.

Then what have we learned from these 2 trials? Although the target systolic BPs were the same in both trials, actual BP reduction was faster and more pronounced in ATACH-2—average systolic BP over the first 24 hours was 120 to 130 mm Hg in ATACH-2 versus 135 to 145 mm Hg in INTERACT-2—and this degree of reduction may have been too much. In fact, systolic BP <130 mm Hg was also associated with worse prognosis in a secondary analysis of INTERACT-2.[4] Taken along with the lack of effect from intensive BP lowering on reducing hematoma expansion observed in both trials, these combined findings argue against overzealous BP lowering during the first few hours after an ICH.

The study by Chung et al[5] published on this issue of *Stroke* contributes another piece to this puzzle. This study evaluated BP variability within the first 24 to 26 after ICH among 386 patients enrolled in the FAST-MAG trial (Field Administration of Stroke Therapy-Magnesium) with a particular interest on BP changes during the first 4 to 6 hours (ie, the hyperacute phase). The first available BP was obtained by paramedics in the field at a median of 23 minutes after symptom onset. The results demonstrate a strong dose-dependent association of greater BP variability with unfavorable functional outcomes (modified Rankin score of 3–6) at 90 days. The association was particularly strong for BP variability during the hyperacute period, to the point that patients in the highest quintile of hyperacute BP variability had a 3- to 4-fold increase in the risk of unfavorable outcome even after adjustment for age, initial severity, and mean systolic BP. Of note, mean systolic BPs during the first 6 hours ranged mostly between 155 and 165 mm Hg, and neither mean systolic BP nor maximal systolic BP during this hyperacute period was associated with unfavorable functional outcome.

Although the analysis by Chung et al[5] could not be adjusted for all major prognostic factors (missing were hematoma volume, hematoma location, and intraventricular hemorrhage), the associations seem solid. Greater BP variability was also associated with worse clinical outcomes in INTERACT-2 and SAMURAI-ICH (Stroke Acute Management With Urgent Risk-Factor Assessment and Improvement–Intracerebral Hemorrhage),[6,7] although these trials did not include consistent information on the BP during the first few hours. Thus, cumulative evidence suggests that BP variability should be avoided, especially very early after an ICH.

What the study by Chung et al[5] cannot tell us is to what degree the BP changes were induced by BP-lowering medications. Neither does it provide information on early

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neurological decline related to the BP changes, which actually were not more common in the intensive treatment arms of INTERACT-2 or ATACH-2. Also, as acknowledged by the investigators and especially considering the limitations of the adjusted analysis, the data cannot conclusively determine whether the association of greater hyperacute BP variability with worse outcome reflects a detrimental effect of the BP fluctuations or simply shows that BP fluctuations are more prominent in patients with more severe hematomas.

The optimal management of acute hypertension after ICH remains undefined. Large randomized trials did not provide consistent evidence that aiming for one particular BP target is broadly beneficial and informed us that very rapid and aggressive BP reduction can be harmful. Meanwhile, exploratory analyses like the one reported by Chung et al[5] indicate that excessive BP fluctuations portend poor outcome and suggest that avoiding these fluctuations could represent a valid therapeutic target. As we keep learning, we should follow the advice of the old sages who always preached the merits of moderation and lower BP after ICH neither too fast nor too low.

Disclosures

None.

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