Seeking best medical treatment for hyperacute intracerebral hemorrhage

Kazunori Toyoda, MD
James C. Grotta, MD

Correspondence to Dr. Toyoda: toyoda@ncvc.go.jp

Neurology® 2015;84:444–445

Although the age-standardized mortality rate for hemorrhagic stroke (intracerebral hemorrhage [ICH] and subarachnoid hemorrhage combined) has decreased worldwide in the past 2 decades, the incidence, number of deaths, and number of disability-adjusted life-years lost continue to increase.[1] Despite having half the incidence of ischemic stroke globally, hemorrhagic stroke causes more deaths and disability-adjusted life-years lost.[1] IV thrombolysis for acute ischemic stroke patients offers an efficient, effective, and evidence-based medical treatment for ischemic stroke. No analogous therapy for patients with acute ICH has been established. Intensive blood pressure (BP) lowering seems to be clinically feasible and potentially safe.[2,3] However, the optimal BP goal for better clinical outcomes remains undetermined. In the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial 2 (INTERACT2),[4] early lowering of systolic BP (SBP) to less than 140 mm Hg showed no definitive difference in percentage of death or major disability at 90 days as a primary endpoint but significantly better modified Rankin Scale scores by ordinal analysis than SBP lowering to less than 180 mm Hg. Thus, the trial provided promising evidence suggesting benefit for early BP lowering in ICH management.

In this issue of *Neurology*®, Arima et al.[5] sought to investigate the clinical effects of intensive SBP lowering in 2,794 patients enrolled in INTERACT2; the therapy appeared beneficial across a wide range of baseline SBP. In addition, an SBP goal of 130–139 mm Hg on average, as well as the same SBP range 1 hour after initiation of therapy, was likely to be maximally beneficial. The risk of poor outcome increased constantly above this range. This result was similar to that from the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement–ICH Study[6] and others. The range of 130–139 mm Hg is much lower than recommended SBP levels in current guidelines on acute ICH management worldwide.[7,8] The mechanisms for the benefits of intensive BP control may include prevention of hematoma growth, edema growth, and acute systemic vascular and organ damage, although hematoma growth did not differ between 2 groups with different SBP goals in INTERACT2.

Although INTERACT2 and its subanalyses, including the present one,[5] have brought us several major scientific findings, the trial leaves unresolved problems. For example, clinical outcomes did not differ between patients with early randomization within 4 hours after symptom onset and those randomized later, although the main focus of the trial was emergent BP lowering during hyperacute ICH.[4] The variation of choice among antihypertensive agents according to different SBP goals might have affected results of the main and substudies. A meta-analysis of INTERACT2 and other trials, including the ongoing Antihypertensive Treatment of Acute Cerebral Hemorrhage II trial,[9] may help resolve these issues and provide a more confident optimal BP goal for patients with acute ICH.

Establishing the efficacy and safety of early intensive BP lowering for patients with ICH will have many benefits beyond the important effect of improving individual patient outcomes. It will provide a stronger rationale for us to promote public education on the need to seek emergency care immediately after noticing stroke symptoms, not only to allow timely reperfusion if stroke is ischemic, but also to undergo immediate intensive antihypertensive therapy if stroke is hemorrhagic. Prehospital initiation of BP lowering may be even more beneficial.[10] Because intensive BP lowering appears to be harmful for hyperacute ischemic stroke patients, development of new screening technologies to differentiate ICH from ischemic stroke in the prehospital setting should be encouraged. Neuroprotective and hemostatic therapies that have proven disappointing so far in patients with ICH should be reevaluated in the ultra-early setting. With the impetus provided by studies such as INTERACT2, we anticipate that the next generation of clinical trialists seeking to find effective pharmacotherapy for hyperacute stroke will be extraordinarily busy.

STUDY FUNDING

No targeted funding reported.

See page 464

From the Department of Cerebrovascular Medicine (K.T.), National Cerebral and Cardiovascular Center, Suita, Japan; and Memorial Hermann Hospital (J.C.G.), Houston, TX.

Go to Neurology.org for full disclosures. Funding information and disclosures deemed relevant by the authors, if any, are provided at the end of the editorial.

DISCLOSURE

The authors report no disclosures. Go to Neurology.org for full disclosures.

REFERENCES

1. Krishnamurthi RV, Feigin VL, Forouzanfar MH, et al. Global and regional burden of first-ever ischaemic and haemorrhagic stroke during 1990–2010: findings from the Global Burden of Disease Study 2010. Lancet Glob Health 2013;1:e259–e281.
2. Anderson CS, Huang Y, Wang JG, et al. Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT): a randomised pilot trial. Lancet Neurol 2008;7:391–399.
3. Koga M, Toyoda K, Yamagami H, et al. Systolic blood pressure lowering to 160 mmHg or less using nicardipine in acute intracerebral hemorrhage: a prospective, multicenter, observational study (the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement–Intracerebral Hemorrhage Study). J Hypertens 2012;30:2357–2364.
4. Anderson CS, Heeley E, Huang Y, et al. Rapid blood-pressure lowering in patients with acute intracerebral hemorrhage. N Engl J Med 2013;368:2355–2365.
5. Arima H, Heeley E, Delcourt C, et al. Optimal achieved blood pressure in acute intracerebral hemorrhage: INTERACT2. Neurology 2015;84:464–471.
6. Sakamoto Y, Koga M, Yamagami H, et al. Systolic blood pressure after intravenous antihypertensive treatment and clinical outcomes in hyperacute intracerebral hemorrhage: the Stroke Acute Management with Urgent Risk-Factor Assessment and Improvement–Intracerebral Hemorrhage Study. Stroke 2013;44:1846–1851.
7. Morgenstern LB, Hemphill JC III, Anderson C, et al. Guidelines for the management of spontaneous intracerebral hemorrhage: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 2010;41:2108–2129.
8. Toyoda K, Steiner T, Epple C, et al. Comparison of the European and Japanese guidelines for the acute management of intracerebral hemorrhage. Cerebrovasc Dis 2013;35:419–429.
9. Qureshi AI, Palesch YY. Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) II: design, methods, and rationale. Neurocrit Care 2011;15:559–576.
10. Ankolekar S, Fuller M, Cross I, et al. Feasibility of an ambulance-based stroke trial, and safety of glyceryl trinitrate in ultra-acute stroke: the rapid intervention with glyceryl trinitrate in Hypertensive Stroke Trial (RIGHT, ISRCTN66434824). Stroke 2013;44:3120–3128.