Hemorrhagic Stroke

The Importance of Acute Hypertensive Response in ICH

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Acute hypertensive response is the elevation of blood pressure (BP) above normal and premorbid values that initially occurs within the first 24 hours of symptom onset in patients with intracerebral hemorrhage (ICH). The acute hypertensive response is characterized by its high prevalence, self-limiting nature, and prognostic significance. To remain consistent with the 2003 World Health Organization/International Society of Hypertension statement, acute hypertensive response is defined as systolic BP (SBP) ≥140 mm Hg demonstrated on 2 recordings taken 5 minutes apart within 24 hours of symptom onset. A total of 33,992 patients (75.0%) had an initial SBP ≥140 mm Hg among 45,330 patients presenting with an ICH analyzed in the National Hospital Ambulatory Medical Care Survey. Acute hypertensive response is usually set on the platform of inadequately treated or undetected chronic hypertension. However, elevation and spontaneous reduction in the initial BP during the next few days support the role of other transient and stroke-specific mechanisms. Presumably, the primary cause of the acute hypertensive response is damage or compression of specific regions in the brain that mediate autonomic control with functional adaptation during the next few days. Hypertensive responses to other factors are exaggerated and additive because of impaired parasympathetic activity and baroreceptor sensitivity. This article addresses the state of knowledge about acute therapy for hypertensive response with ICH.

The treatment of acute hypertensive response in ICH has been controversial for the past 3 decades. The Figure demonstrates the 4 periods of evolution in our understanding of pathophysiology and treatment. The current notion of treatment is based on the observation that one third of the subjects presenting with ICH demonstrate hematoma expansion (with subsequent deterioration and death) in the first few hours after onset. An initial SBP of ≥200 mm Hg is associated with hematoma expansion, perihematoma brain edema formation, and increased mortality among patients with an ICH. Recent studies suggest that reduced metabolism (hibernation) and preserved autoregulation in the perihematoma region may prevent any ischemic injury associated with SBP reduction. The current American Stroke Association and European Stroke Initiative guidelines recommend reduction and maintenance of SBP <180 mm Hg in patients with an ICH. A lower limit for safe reduction is undefined. Both guidelines acknowledge that there may be a subset of patients who can tolerate more aggressive SBP reduction, such as those with good neurological status or without chronic hypertension. Treatment of acute hypertensive response has been subsequently incorporated as 1 of the 26 quality indicators related to 18 facets of care to quantify the appropriateness of medical care. The ICH-specific intensity of care quality metrics includes treatment with intravenous antihypertensive medication for 24 hours after Emergency Department arrival for elevated BP (SBP ≥180 mm Hg) as a quality parameter on the basis of its high prevalence and guidelines from professional organizations. The performance is scored as 1, if SBP target goal is reached within 2.5 hours of the second of the 2 consecutive measurements or not applicable, and 0, if SBP target range is not achieved. Treatment success is defined as target BP range achieved within 2.5 hours of elevated BP detection (on the basis of the time interval between 2 consecutive SBP ≥180 mm Hg and first SBP <180 mm Hg recordings). Actual lowering of SBP and not the treatment goal specified was chosen because actual lowering is associated with lower rates of hematoma expansion and death and disability at 3 months in a previous study. SBP was used to define treatment target because the present evidence supports the association between SBP and hematoma expansion. No clear relationship with diastolic BP has been demonstrated. Interestingly, SBP in patients with an ICH demonstrates greater variability and large magnitude changes with less prominent changes in diastolic BP. Thus, both diastolic BP and mean arterial pressure may underestimate dynamic changes in BP in the first 24 hours of ICH. The quality metrics recommend adequate SBP control with an infusion for 24 hours after initiation of treatment (24–27 hours after symptom onset), to provide adequate SBP control during the time that hematoma expansion will mostly occur. Although the rate of hematoma expansion is highest in the first 3 hours after symptom onset, expansion occurs in 12% to 37% of patients between 3 and 24 hours after symptom onset. Early termination of antihypertensive treatment may lead to poor control of SBP, with subsequent increase in delayed bleeding. In a validation study, the score on intensity of care quality metrics in 50 consecutive patients with an ICH ranged from 17 to 26 points. Survival of patients with an ICH was different in tertiles on the basis of the performance score with highest survival among tertile of highest score on the intensity of care quality metrics (100%, 67%, and 55%; P = 0.017). The receiver operator curve...
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Demonstrated a high discriminating ability of intensity of care quality metrics for in-hospital mortality (receiver operator curve value, 0.73; 95% confidence interval, 0.6-0.87). In an exploratory analysis, we adjusted for age, hematoma volume, initial Glasgow Coma Scale score, and intraventricular hemorrhage. After adjusting for markers of disease severity, higher total score on ICH-specific intensity of care quality metrics continued to demonstrate a relationship with lower in-hospital mortality (odd ratio, 0.72; 95% confidence interval, 0.48-1.06). However, further studies will be required to determine whether intensity of care or relative lack of response to treatment because of severity of disease accounts for this relationship. The current preliminary data support SBP treatment as a valuable part of intensity of care among patients with an ICH independent of markers of disease severity.

More aggressive SBP lowering was initially considered because an observational study suggested that more aggressive SBP reduction may have greater benefit in reducing the rate of hematoma expansion. The rate of hematoma expansion was 9% in patients with SBP<150 mm Hg and 30% among patients treated to maintain SBP<160 mm Hg or a higher threshold. The National Institute of Neurological Disorders and Stroke-funded Antihypertensive Treatment of Acute Cerebral Hemorrhage (ATACH) trial was a multicenter open-labeled pilot trial to determine tolerability and safety of 3 escalating levels of antihypertensive treatment goals for acute hypertensive response in 60 subjects with supratentorial ICH within 6 hours of symptom onset. The observed proportions of neurological deterioration and serious adverse events were below the prespecified safety thresholds, and the 3-month mortality rate was lower than expected in all SBP tiers, including the most aggressive treatment tier (to reduce and maintain SBP<140 mm Hg). The Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage (INTERACT) study was an investigator-initiated, blinded outcome, randomized trial that randomized 404 patients with ICH with elevated SBP (≥150 and <220 mm Hg) to either intensive BP management (SBP<140 mm Hg) or American Stroke Association-guideline-based BP management (SBP<180 mm Hg) using available antihypertensive agents. Relative risk of hematoma growth ≥33% or ≥12.5 mL was 36% lower in the intensive group than in the American Heart Association-guideline-based BP management group. In subgroup analyses, patients recruited within 3 hours and patients with an initial SBP≥181 mm Hg seemed to have the greatest benefit with intensive SBP reduction.

After the ATACH I trial proved the feasibility and tolerability of intensive SBP reduction, the INTERACT study demonstrated attenuation of hematoma expansion with intensive SBP reduction, 2 phase III trials were initiated. In the last quarter of 2007, the INTERACT phase III was initiated that combined the data derived from the vanguard phase and the main phase to perform the final analysis with adequate power. The trial recruited 2800 patients with acute ICH from >140 centers. The data are being analyzed and anticipated to be published in 2013. The primary objective of the ATACH II initiated in 2010 was to determine the efficacy of intensive BP reduction for acute hypertensive response in 1280 subjects with supratentorial ICH. The primary hypothesis of the trial is that intensive SBP reduction (SBP<140 mm Hg) using intravenous nicardipine infusion for 24 hours post randomization reduces the proportion of death and disability at 3 months by >10% compared with standard BP reduction (SBP<180 mm Hg) among patients with ICH treated within 4.5 hours of symptom onset. The ATACH II will provide critically unique information to address whether the benefit or lack of benefit is either augmented or unchanged in patients treated within 4.5 hours, those with SBP≥180 mm Hg, or those treated with a single agent and achieving target SBP at a high rate. The ATACH study will also provide information about any differential effect between populations, or because of overall intensity of care or threshold for treatment.

The results of the ongoing studies will have direct implications for 75% of the patients with ICH. SBP treatment is a strategy that can be made widely available without specialized equipment or personnel, and can make a major impact on outcome in patients with ICH. In a post hoc analysis of ATACH I, we evaluated the effect of SBP reduction (relative to initial SBP) on poor 3-month outcome (defined as a modified Rankin scale score of 4-6) to derive estimates of treatment benefit. The median SBP reduction was 62 mm Hg at 6 hours from treatment initiation. The frequency of poor 3-month outcome was 48% versus 35% in patients having (<62 mm Hg) versus equal to or more than the median SBP reduction (≥62 mm Hg) at 6 hours (absolute reduction of 13%). The lower rate of poor outcome at 3 months was probably attributed to the lower rate of hematoma expansion in patients with SBP reduction of ≥62 mm Hg (median value).
at 6 hours from treatment (21% versus 31%, a 10% absolute reduction). A prominent reduction in morbidity and mortality may be possible if estimates of treatment effect from our current pilot trial are accurate.

**Disclosures**

Dr Qureshi has received funding from the National Institutes of Health RO1-NS44976-01A2 (medication provided by ESP Parma), American Heart Association Established Investigator Award 0840053N, National Institute of Health U01-NS062091-01A2, and the Minnesota Medical Foundation, Minneapolis, MN.

**References**


**Key Words:** acute hypertensive response ▪ blood pressure ▪ clinical trials ▪ hypertension ▪ intracerebral hemorrhage ▪ stroke
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Stroke. 2013;44:S67-S69
doi: 10.1161/STROKEAHA.111.000758
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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