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Intensive Blood Pressure Lowering in Intracerebral Hemorrhage

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THE CASE

A 55 year-old man presents within 2 hours of acute left-sided weakness. Head CT reveals a 60 ml right thalamic hemorrhage. Blood pressure (BP) upon presentation is 150/95 mmHg.

THE QUESTIONS

Should BP be lowered? If yes, what is the target BP and which anti-hypertensive agents should be used?

THE CONTROVERSY

Intensive BP Lowering in Intracerebral Hemorrhage BP Should Be Lowered

Craig Anderson—As the on-call stroke neurologist, I would treat this patient according to an approved ‘management of intracerebral hemorrhage (ICH)’ protocol readily available on the hospital intranet and my decision-support tool. The patient is high-risk for poor outcome – early presentation, large hematoma, deep location – and early, rapid and sustained control of elevated systolic blood pressure (SBP, target <140mmHg) has ‘reasonably strong’ supporting evidence of benefit on functional outcome, without significant harm [1].

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Disclosures

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Moreover, BP lowering is a component of active care, with avoidance of early do-not-resuscitate (or palliative care) orders.

I recognize that clinicians require level 1, or grade A, quality information from research that is scientifically robust, current, and closely matches the patients they encounter in routine practice. However, generating randomized evidence for decision-making in ICH is complex due to its low rate compared to acute ischemic stroke, heterogeneous etiology, high early mortality, and variable involvement of neurosurgery.

Although the clinical association of high BP and adverse outcomes in ICH is common, there has been longstanding concern that rapid BP lowering can cause cerebral ischemia, especially if cerebral autoregulation is altered from chronic hypertension or brain injury. However, focused studies have not confirmed any such harm by showing no significant relationship between BP lowering and cerebral blood flow or oxygenation in the perihematomal region or cerebral hemispheres in ICH patients [2].

Failure to provide a clear effect on the primary outcome of early intensive BP lowering compared to contemporaneous BP management (SBP <180 mmHg) in 2,839 ICH patients with high SBP (150–220 mmHg) in the main phase, Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT2) [3], and apparent conflicting results with the second Antihypertensive Treatment for Acute Cerebral Hemorrhage (ATACH-II) trial [4], have likely tempered enthusiasm for rapid BP lowering in ICH. The borderline significant reduction in death or disability (modified Rankin scale [mRS] score 3 to 6 at 90-days) in the intensive group (odds ratio [OR] 0.87, 95% confidence interval [CI] 0.75–1.01; P=0.06) and significantly better functional recovery (OR for greater disability 0.87, 95%CI 0.77–1.00; P=0.04) on an ordinal shift analysis of mRS scores, indicates INTERACT2 was unfortunately under-powered.

In a comparison of ‘very early’ (<4.5 hours) and ‘very rapid and intensive’ (SBP <140 mmHg) with standard (SBP <180 mmHg) BP management, the ATACH-II trial [4] showed no between-group difference in the frequency of death or disability (mRS scores 4 to 6) at 90 days (adjusted relative risk [RR] 1.04, 95% CI 0.85–1.27; P=0.72). However, more renal adverse events emerged over 7 days (9.0% vs. 4.0%; P=0.002) and serious adverse events were borderline significantly increased in the intensive group at 90 days (adjusted RR 1.30, 95% CI 1.00–1.69; P=0.05).

Making sense of the conflicting results of INTERACT2 and ATACH-II requires sensible consideration of differences in their BP management protocols. First, all ATACH-II patients had elevated SBP at presentation (mean 200 mmHg) and most received BP lowering treatment before randomization, whereas few INTERACT2 participants had this level of SBP at presentation. Second, ATACH-II participants were administered intravenous nicardipine, whilst INTERACT2 participants received a range of intravenous and oral BP lowering agents based on local availability. Third, the achieved mean minimum SBP (<130 mmHg) in the intensive treatment and BP level (<110 mmHg) for cessation of intravenous BP lowering treatment were lower in ATACH-I compared to INTERACT2. A sub-analysis of INTERACT2 indicates the best outcome from ICH is related to an achieved mean SBP of

130–139 mmHg over 24 hours, but a modest increase in poor outcome was suggested at SBP <130 mmHg [5]. These differences imply that very rapid and intensive SBP treatment (target <130 mmHg) for ICH patients with very high SBP could negate any potential benefits.

Subsequent meta-analysis of randomized trials, and additional information of intensive BP lowering in surgical patients [6], provides further confirmation of safety and a compelling trend towards a benefit of early intensive BP lowering in ICH, supported by a significant effect on the most plausible, mechanistic surrogate endpoint of hematoma growth [7].

BP Should Not Be Lowered

Adnan Qureshi—The value of pharmacologically reducing blood pressure in this patient is questionable because the relationship between acute hypertensive response and hematoma expansion [8] and mortality [9] is evident at much higher SBP in patients with ICH. Kazui *et al.* [8] reported that relationship between acute hypertensive response and hematoma expansion was evident when SBP was ≥200 mmHg on admission. The Intensive BP reduction in acute cerebral hemorrhage trial (INTERACT) [10] reported that early intensive blood pressure reduction resulted in the most prominent reduction in hematoma expansion with an initial systolic blood pressure ≥181 mmHg. Therefore, using SBP value of ≥150 mmHg to reduce BP such as in this patient may lack clinical relevance. Such patients may not even require pharmacological reduction of systolic blood pressure because of spontaneous reduction in SBP. Only 66% of patients required any intravenous antihypertensive medication in INTERACT-2 when patients with SBP measurements ≥150 mmHg were included [3]. A higher threshold for treatment such as SBP >180 mmHg used in ATACH-2 trial [4] ensured 99.5% of patients randomized required IV antihypertensive medication.

American Stroke Association guideline state acute lowering of SBP to 140 mmHg, in ICH patients with admission SBP between 150 and 220 mmHg who have no contraindication for BP lowering, is safe and may improve functional outcome [1]. It should be noted that main evidence for this recommendation is derived from reduction in death or disability at 3 months post randomization observed in INTERACT-2 in patients randomized to intensive treatment (lowering and maintaining SBP to <140 mmHg) [4]. However, the SBP profile in intensive treatment group was a reflection of SBP values closer to 140 mmHg rather than lower SBP values (only 33.4% achieving the target SBP of <140 mmHg at 1 hour post randomization) [11]. A post hoc analysis of INTERACT-2 also identified that that patients with lowest odds of death and disability at 3 months post randomization had average SBP of 130 mmHg at selected time points within 24 hours of randomization [3]. There was no difference in death or disability rates at 3 months post randomization in ATACH-2 trial among patients randomized to standard treatment (SBP mean minimum systolic blood pressures during the first 2 hours 141.1 (±14.8) mmHg) compared with intensive treatment (128.9 (±16) mmHg) but intensive treatment was associated with a higher rate of renal related adverse events [4]. Therefore, maintaining the SBP between 130–150 mm Hg may be best supported by current evidence and is relatively consistent with American Stroke Association guidelines.

Intravenous nicardipine would be the preferred intravenous agents with rapid onset (5–10 minutes) and short duration of action (half-life 30 minutes to 4 hours) to allow precise titration [12]. Intravenous nicardipine has not resulted in measurable exacerbation of intracranial pressure in clinical studies unlike hydralazine or nitroprusside. The intravenous infusion is initiated at a rate of 5 mg/hr and increased by 2.5 mg/hr increments every 15 minutes until the maximum dose of 15 mg/hr or target blood pressure is reached. Once the target blood pressure is reached, the infusion rate is to be adjusted by 1 to 2.5 mg/hr to maintain blood pressure in the specified range. Availability of pre-mixed infusion bags and widespread experience among emergency department and intensive care unit staff has allowed initiation of intravenous nicardipine in time sensitive manner and titration based on regular automated blood pressure cuff measurements. Appropriate hydration of patients with intravenous isotonic fluids is essential to avoid greater than expected reduction in SBP during initiation of intravenous nicardipine.

Rebuttal by Dr. Anderson: Dr Qureshi fails to appreciate the evidence for a direct continuous association of increasing SBP and adverse outcomes in ICH. Limiting treatment to patients with SBP >180 mmHg will reduce workload, but denies many more of potential benefit in a critical illness where there is no other therapy with a similar or stronger, evidence-base. There are often hypotheses proposed as to why a treatment might be more or less effective in patients according to certain characteristics, but the rule is that interventions generally produce similar directions of effect and comparable magnitudes of relative effects. This has been clearly demonstrated in INTERACT2 where the magnitude of the ‘intention-to-treat to <140mmHg’ effect of BP lowering was consistent across all levels of presenting SBP over 150 mmHg. Moreover, contrary to ATACH-II, the INTERACT2 protocol was safe in all types of ICH, including patients with moderate-severe renal failure (1 in 10 patients), cerebral atrophy and other markers of brain frailty, and those with very high presenting levels (and consequently, largest drop with treatment) of SBP.

He ignores the totality of clinical trial data, which includes ATACH-II, of an effect of early BP lowering on hematoma growth, and by implying that one can delay intervening until a patient has deteriorated to a higher SBP, counters all philosophy of modern acute stroke care.

Finally, there is no evidence to support his claim that nicardipine provides clear advantages over any other intravenous antihypertensive agent, or even use of a topical nitrate patch.

Rebuttal by Dr. Qureshi: Caution has to be used even when recommending a target SBP of 130–139 mmHg for ICH patients with acute hypertensive response based on post hoc analysis of INTERACT 2 trial. In the post hoc analysis, subjects with a post randomization SBP of 130–139 mmHg with 24 hours postrandomization had the lowest rates of death or disability compared with those with higher SBP post randomization. However, it should be noted that subjects with higher postrandomization SBP had higher pretreatment National Institutes of Health Stroke Scale scores, hematoma volumes, and SBP and thus were more likely to experience death or disability independent of SBP reduction to a specific value. Compared with postrandomization SBP of 130 mmHg, there was a non-significant increase in the risk of death or disability was seen at 120 mmHg (odds ratio 1.3, 95% confidence

interval 0.92–1.8). Therefore, the therapeutic target of the <140 mm Hg for SBP without specifying parameters for the pretreatment SBP and patient characteristics should not be recommended. Both INTERACT 2 and ATACH-2 were not a representation of patients with low Glasgow Coma scale scores and large intraparenchymal hematomas. Therefore, caution is required prior to assuming the safety of intensive SBP lowering in such patients with presumably high regional or global intracranial pressures.

Comments by Drs. Selim and Molina: Let's face it! This is clearly a debate about the seemingly contradictory results of the largest trials investigating intensive BP lowering following acute ICH – INTERACT-2 and ATACH-2. Unwillingly and unavoidably, ATACH-2 and INTERACT-2 became wedded to each other, and no discussion of either trial is complete without including the other. The two trials randomized patients with acute spontaneous ICH to SBP target of <140 to <180 mmHg, but unlike INTERACT-2 which suggested that lowering SBP to a target of ≤140 mmHg is safe and beneficial (albeit the benefit was modest and marginal), ATACH-2 casted doubt on the safety and efficacy of intensive SBP lowering to <140 mmHg. However, the initial objectives of ATACH-2 might have been unintentionally influenced midway through its course by the results of its predecessor, INTERACT-2. When ATACH-2 started, practice guidelines' recommended SBP target was 160–180 mmHg. ATACH-2 allowed treatment of BP to be initiated before randomization to lower SBP to <180 mmHg and patients were not eligible if SBP was reduced to <140 mmHg before randomization. After INTERACT-2, a new target SBP of ≤140 mmHg was adopted and this change in practice likely resulted in more aggressive lowering of SBP closer to 140 mmHg. A closer look at the data from INTERACT-2 and ATACH2 clearly shows that SBP during the first 24 hours was approximately 120s mmHg in the intensive-treatment group and 140s mmHg in the standard-treatment group in ATACH-2 vs. 140s to 150s mmHg and 160s mmHg, respectively, in INTERACT-2. In other words, ATACH-2 truly compared intensive vs. "ultra" intensive BP in ICH. Therefore, the results of these two trials are not necessarily contradictory. Like INTERACT-2, ATACH-2 supported the safety of SBP lowering to 140 mmHg. In addition, ATACH-2 showed that more aggressive lowering of BP is not of added benefits and was harmful. In light of this data, we would support the use of any anti-hypertensive agent, other than nitroprusside, to decrease SBP to 140 mmHg, but not much lower, in acute ICH patients.

So, should we lower our patient's SBP to 140 mmHg? Perhaps, but we really don't know if we should. Our patient has a large 60 ml ICH and is at increased risk for cerebral hypoperfusion with BP lowering due to high intracranial pressure, and both trials enrolled very few patients with large ICH to provide evidence-supported guidance. The controversy of BP lowering in acute ICH still goes on!

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