Degree and Timing of Intensive Blood Pressure Lowering on Hematoma Growth in Intracerebral Hemorrhage

Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2 Results

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Background and Purpose—Degree and timing of blood pressure (BP) lowering treatment in relation to hematoma growth were investigated in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial-2 (INTERACT2).

Methods—INTERACT2 was an international clinical trial of intensive (target systolic BP [SBP], <140 mm Hg) versus guideline-recommended (SBP, <180 mm Hg) BP lowering in 2839 patients within 6 hours of spontaneous intracerebral hemorrhage and elevated SBP (150–220 mm Hg), in which 964 had repeat cranial computed tomography at 24 hours. ANCOVA models assessed categories of SBP reduction and time to target SBP on 24-hour hematoma growth.

Results—Greater SBP reduction was associated with reduced hematoma growth (13.3, 5.0, and 3.0 mL for <10, 10–20, and ≥20 mm Hg, respectively; *P* trend<0.001). In the intensive treatment group (n=491), the least mean hematoma growth was in patients who achieved target SBP <1 hour (2.6 mL) versus to those in target at 1 to 6 (4.7 mL) and >6 hours (5.4 mL). The smallest mean absolute hematoma growth (2.0 mL) was in those achieving target SBP 5 to 8 times versus 3 to 4 (3.1 mL) and 0 to 2 times (5.2 mL).

Conclusions—Intensive BP lowering with greater SBP reduction, which is achieved quickly and maintained consistently, seems to provide protection against hematoma growth for 24 hours.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00716079.

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Elevated systolic blood pressure (SBP) is common after acute spontaneous intracerebral hemorrhage (ICH). Attenuation of hematoma growth is the most plausible mechanism for any beneficial effect of intensive BP lowering, but this was not confirmed in the Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage Trial (INTERACT),[1,2] leaving uncertainty over any heterogeneity of the treatment by timing and degree of BP lowering. We assessed the effects of degree and consistency of BP lowering on hematoma growth in INTERACT2 participants.

Materials and Methods

INTERACT2 was an international, multicenter, open, blinded end point, randomized controlled trial, as described elsewhere.[2] In brief, 2839 spontaneous ICH patients (<6 hours of onset) and elevated SBP (150–220 mm Hg) were randomly assigned to intensive (target SBP, <140 mm Hg within 1 hour) or guideline-recommended (target SBP, <180 mm Hg) BP lowering.[3] The study is registered with ClinicalTrials.gov, number NCT00716079.

Demographic and clinical characteristics were recorded, including SBP every 15 minutes in the first hour post randomization and 6 hourly until 24 hours; the number of readings <140 mm Hg were

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*A list of all INTERACT2 study participants is given in online-only Data Supplement.

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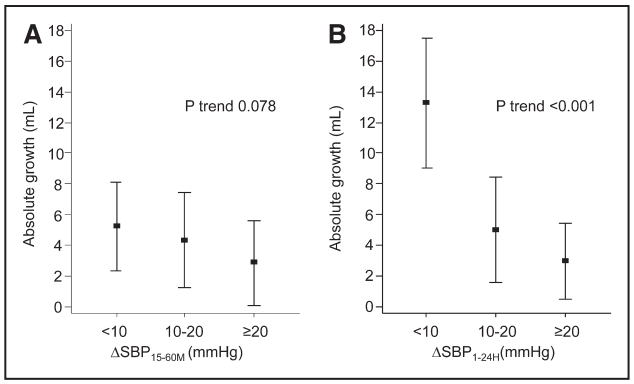

Figure 1. Effect of blood pressure (BP) reduction on hematoma growth by time and absolute hematoma growth stratified by baseline systolic BP (SBP). Data are adjusted by age, sex, Chinese region of recruitment, previous intracerebral hemorrhage (ICH), hematoma location, baseline hematoma volume, baseline SBP, time from ICH onset to baseline computed tomographic scan, and randomized treatment.

noted. In a substudy, baseline and 24±3-hour computed tomographic brain scans were performed and analyzed centrally.

ANCOVA models assessed associations of SBP reduction on 24-hour hematoma growth.

Results

Among 2839 participants of the INTERACT2 study, 964 (40%) were included in the computed tomographic substudy. Compared with patients without a follow-up computed tomography, they were more often on anticoagulation or antiplatelet therapy, had higher National Institute of Health Stroke Scale scores, and shorter time from symptoms onset to randomization at baseline (Table I in the online-only Data Supplement). However, the 2 groups were similar with regard to baseline SBP, ICH volume and location, and allocation to intensive BP-lowering treatment. Table II in the online-only Data Supplement shows the patient characteristics by the degree of SBP reduction: those with the smallest ΔSBP (<10 mm Hg) were older and those with greatest ΔSBP (≥20 mm Hg) were more often women, with a history of ICH, higher baseline BP, and more often included to intensive BP-lowering group (420 [59%]; P<0.001). A greater degree of SBP reduction was associated with less hematoma growth: $\Delta SBP_{1-24\ h}$ at <10-, 10- to 20-, and ≥20-mm Hg reduction was associated with hematoma growth (mL) of 13.3 (9.0–17.5), 5.0 (1.6–8.4), and 3.0 (0.5–5.4), respectively (P trend<0.001). A similar trend was observed for the same degrees of $\Delta SBP_{15-60\ mol/L}$, but this was not statistically significant (Figure 1). There was no significant difference in the relation of SBP reduction and hematoma growth in patients with baseline SBP levels above or below 180 mm Hg for any of $\Delta SBP_{1-24\ h}$ or $\Delta SBP_{15-60\ mol/L}$ (P homogeneity=0.133 and 0.999, respectively; Table III in the online-only Data Supplement). The results were similar in a sensitivity analysis stratified for trial treatment without any heterogeneity (Table IV in the online-only Data Supplement).

Table V in the online-only Data Supplement shows the participants' baseline characteristics, which are grouped by time from symptom onset to randomization and were broadly similar between groups, except more patients allocated intensive treatment were on anticoagulation in at 3 to 4.5 hours. There was no association of intensive treatment with hematoma growth in these subgroups by time to treatment in crude or adjusted models (P trend=0.691 and 0.702, respectively; Figure 2; Table VI in the online-only Data Supplement).

Of 491 patients randomized to intensive BP lowering, the SBP target was achieved in 242 (49%) and 125 (25%) <1 and 1 to 6 hours, respectively; 124 (25%) did not achieve target <6 hours. The least hematoma growth (mL) was in those achieving target SBP early (≤1 hour; 2.6; 95% confidence interval, 0.1–5.2) compared with later periods 1 to 6 hour (4.7; 95% confidence interval, 1.8–7.5) and >6 hours (5.4; 95% confidence interval, 2.4–8.3; P trend=0.029; Figure 3A).

Hematoma growth was 5.2 (95% confidence interval, 2.7–1.8), 3.1 (0.3–6.0), and 0.4 (–1.1 to 5.1), respectively, according to 0 to 2, 3 to 4, and 5 to 8 times to target SBP (P trend=0.018; Figure 3B).

Discussion

These analyses of INTERACT2 show that a greater fall in SBP was associated with less hematoma growth, irrespective of whether patients received intensive or guideline-based BP-lowering treatment. Patients with the least hematoma growth were those who achieved target SBP of <140 mm Hg within the first hour and in those who sustained this target throughout the first 24 hours. These data are relevant for patient management, where early, intensive, and consistent lowering of SBP seems to offer the greatest potential to improve outcome in ICH, including better functional recovery in those with smooth BP control.[4] These results also support recent guideline recommendations for more intensive BP management in ICH.

Outcome in ICH depends on the size and growth of the underlying hematoma,[5,6] which are related to mechanisms of

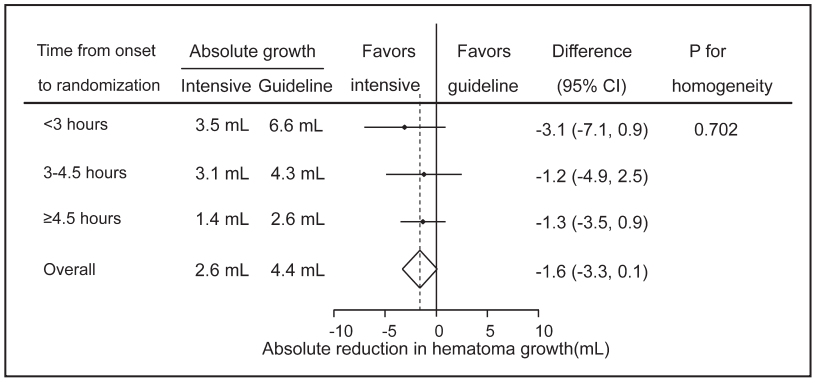

Figure 2. Treatment effect on hematoma growth by time. Time indicates date and time of intracerebral hemorrhage onset to date and time of randomization, adjusted by baseline hematoma volume and hematoma location.

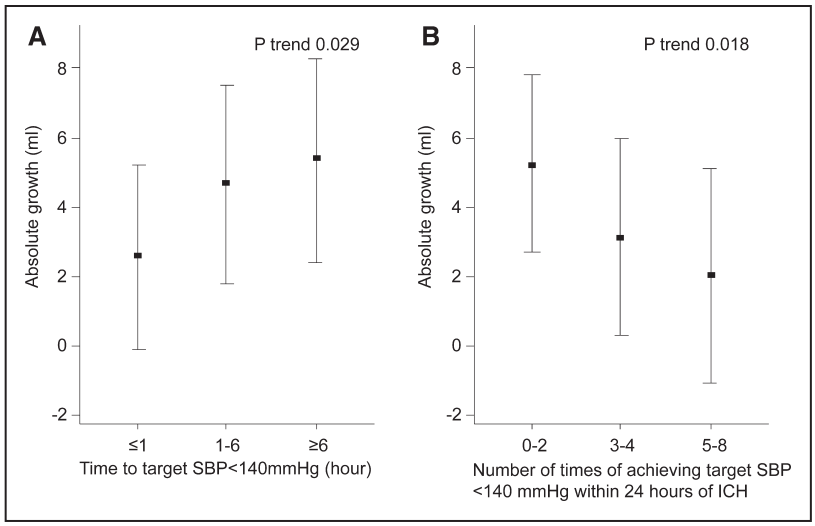

Figure 3. A, The effect of time to treatment target systolic blood pressure (SBP) <140 mm Hg on hematoma growth among patients in the intensive treatment group. Data are adjusted by age, sex, Chinese region, previous intracerebral hemorrhage (ICH), hematoma location, baseline hematoma volume, baseline SBP, and time from ICH onset to baseline computed tomographic (CT) scan. **B**, The effect of the number of times SBP achieved treatment target SBP within 24 hours on hematoma growth among patients in the intensive treatment group. Data are adjusted by age, sex, Chinese region, previous ICH, hematoma location, baseline hematoma volume, baseline SBP, and time from ICH onset to baseline CT scan.

intravascular hydrostatic pressure, local tissue pressure, and mechanical injury to brain tissue and blood vessels, cerebral blood flow, plasma protein induction, and inflammation.[7,8] Other important factors that may influence hematoma growth include timing of imaging and baseline hematoma volume. Greater SBP reduction and shorter time to target SBP being associated with the least hematoma growth could be related to intensive BP lowering producing larger and faster decreases in intravascular hydrostatic pressure secondary arteriolar rupture. This analyses could not confirm the other mechanisms stated above. Our earlier analyses have shown a linear relationship between achieved SBP and disability in both the hyperacute (1–24 hours) and acute (2–7 days) phases,[9] and similar findings have been reported in other populations.[10,11]

Although our study included a large and heterogeneous population with rigorous prospective and systematic evaluations of both BP and hematoma growth, the analyses are limited by selection bias, inability to establish a causal relationship with treatment, and in being post hoc and not prespecified.

In conclusion, these analyses suggest potential beneficial effects of early and controlled BP-lowering treatment through attenuation of hematoma growth.

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