Effects of Early Intensive Blood Pressure-Lowering Treatment on the Growth of Hematoma and Perihematomal Edema in Acute Intracerebral Hemorrhage

The Intensive Blood Pressure Reduction in Acute Cerebral Haemorrhage Trial (INTERACT)

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Background and Purpose—The Intensive Blood Pressure Reduction In Acute Cerebral Haemorrhage Trial (INTERACT) study suggests that early intensive blood pressure (BP) lowering can attenuate hematoma growth at 24 hours after intracerebral hemorrhage. The present analyses aimed to determine the effects of treatment on hematoma and perihematomal edema over 72 hours.

Methods—INTERACT included 404 patients with CT-confirmed intracerebral hemorrhage, elevated systolic BP (150 to 220 mm Hg), and capacity to start BP-lowering treatment within 6 hours of intracerebral hemorrhage. Patients were randomly assigned to an intensive (target systolic BP 140 mmHg) or standard guideline-based management of BP (target systolic BP 180 mm Hg) using routine intravenous agents. Baseline and repeat CTs (24 and 72 hours) were performed using standardized techniques with digital images analyzed centrally. Outcomes were increases in hematoma and perihematomal edema volumes over 72 hours.

Results—Overall, 296 patients had all 3 CT scans available for the hematoma and 270 for the edema analyses. Mean systolic BP was 11.7 mm Hg lower in the intensive group than in the guideline group during 1 to 24 hours. Adjusted mean absolute increases in hematoma volumes (mL) at 24 and 72 hours were 2.40 and 0.15 in the guideline group compared with −0.74 and −2.31 in the intensive group, respectively, an overall difference of 2.80 (95% CI, 1.04 to 4.56; P = 0.002). Adjusted mean absolute increases in edema volumes (mL) at 24 and 72 hours were 6.27 and 10.02 in the guideline group compared with 4.19 and 7.34 in the intensive group, respectively, for an overall difference of 2.38 (95% CI, −0.45 to 5.22; P = 0.10).

Conclusion—Early intensive BP-lowering treatment attenuated hematoma growth over 72 hours in intracerebral hemorrhage. There were no appreciable effects on perihematomal edema. (Stroke. 2010;41:307-312.)

Key Words: blood pressure ■ clinical trial ■ hypertension ■ intracerebral hemorrhage ■ treatment

Acute intracerebral hemorrhage (ICH) is estimated to affect >1 million people worldwide each year,1 most of whom either die or are left seriously disabled.1,2 Early elevation of blood pressure (BP) is very common after ICH3 and a number of observational studies have demonstrated strong associations between increasing levels of BP and poor outcomes.4–7 The adverse effects of high BP levels on outcomes in ICH are likely to involve a number of different
mechanisms: elevated hydrostatic pressure at the site of the bleed is likely to result in a larger initial hemorrhage with more rapid development of, and ultimately greater, hematoma volume, whereas elevated BP may increase the likelihood of surrounding cerebral edema. Thus, early intensive BP lowering has the potential to reduce growth in both hematoma and perihematomal edema, which may translate into beneficial effects in patients with acute ICH.

The Intensive Blood Pressure Reduction In Acute Cerebral Haemorrhage Trial (INTERACT) pilot phase was a randomized controlled trial that demonstrated that early intensive BP lowering was clinically feasible, well tolerated, and appeared to reduce hematoma growth in patients treated within 6 hours after the onset of acute ICH. The previous report on the beneficial effects of early intensive BP lowering was limited to hematoma growth over 24 hours. In this article, we provide additional information about the effects of early intensive BP lowering on hematoma growth over 72 hours. We also investigated the effects of this treatment on perihematomal edema in acute ICH.

**Methods**

**Study Design and Participants**

The design of the INTERACT has been described in detail elsewhere. Briefly, 404 patients were recruited from a network of hospital sites in China, South Korea, and Australia during 2005 and 2007. Eligible patients were aged ≥18 years with CT-confirmed spontaneous ICH and elevated systolic BP (≥2 measurements of ≥150 mm Hg and ≤220 mm Hg recorded ≥2 minutes apart) with the capacity to start randomly assigned BP-lowering treatment within 6 hours of ICH in a suitably monitored environment. Exclusion criteria were a clear indication for, or contraindication to, intensive BP lowering; ICH secondary to a structural cerebral abnormality or the use of a thrombolytic agent; recent ischemic stroke; deep coma; significant prestroke disability or medical illness; and early planned neurosurgical intervention. The study protocol was approved by the appropriate ethics committee at each participating site. Written informed consent was obtained from each patient or their legal surrogate in situations in which they were unable to do so.

Patients were randomly assigned to receive either an early intensive BP-lowering treatment strategy or the recommended best practice standard of BP lowering at the time, that of the American Heart Association guidelines published in 1999. For patients allocated to the intensive group, the goal was to achieve a systolic BP of 140 mm Hg within 1 hour of randomization and subsequently to maintain this target level for the next 7 days. For patients allocated to the guideline group, treatment was recommended to achieve a target systolic BP of 180 mm Hg. Vital signs were measured according to a protocol with BP recorded in the nonparetic arm with the patient supine using an automated device. Assessments including the Glasgow Coma Scale and the National Institutes of Health Stroke Scale were performed on enrollment; at 24 and 72 hours; and at 7, 28, and 90 days after randomization.

**Outcomes**

The outcomes for the present investigation were the absolute and proportional increases in hematoma and perihematomal edema volumes during the first 72 hours after ICH. Sites were required to perform CT scans on patients according to standardized techniques at baseline and at 24±3 and 72±3 hours after the initial CT; these time points were chosen to assess the primary effects of treatment on hematoma and edema growth, respectively. If the 24-hour CT scan was not done within the specified time period, this assessment was replaced by the first available scan during 27 to 48 hours or by the last available scan during 6 to 21 hours if this was the only CT scan available. If the 72-hour CT scan was not done within the specified time period, this assessment was replaced by the first available scan during 75 to 80 hours or by the last available scan during 48 to 69 hours. For each patient, uncompressed digital images were sought by the analysis laboratory in DICOM format on a CD-ROM identified only by the patient’s unique study number. Hematoma and perihematomal edema volumes were calculated independently by 2 trained neuroradiologists who were blind to clinical data, treatment, and date and sequence of the scan using computer-assisted multislice planimetric and voxel threshold techniques in MiStar Version 3.2 (Apollo Medical Imaging Technology, Melbourne, Australia). Interreader reliability was tested by reanalysis of 10% of CT scans by both readers after 30% and 60% of the scans were completed to avoid drift (intraclass correlation coefficient, 0.97; 95% CI, 0.95 to 0.98 for hematoma volume; and 0.91; 95% CI, 0.87 to 0.94 for edema volume). For the small number of CT scans received as digital images or plain films, hematoma volume was measured manually using the ABC/2 method; perihematomal edema volume was not estimated by this method and such data were noted as missing.

**Statistical Analysis**

The effects of early intensive BP lowering on absolute and proportional changes in hematoma or edema volumes at 24 or 72 hours after the initial CT were assessed by an analysis of covariance with hematoma location, baseline hematoma volume, and time from ICH to CT included as covariates. Differences between treatment groups in absolute or proportional increases over 72 hours were ascertained by generalized estimating equations using increases in hematoma or edema volumes as repeat measures with the same covariates.
Relative changes in hematoma and edema volumes were log-transformed to remove skewness after addition of the value 1.1 to eliminate negative values. To explore differential treatment effects across varying ICH characteristics, the frequencies of patients according to absolute increase in hematoma or edema volumes at 24 or 72 hours were compared between randomized groups using ordinal logistic regression models. Differences in BP were tested at specific time points using a t test. P<0.05 was considered statistically significant. This study was registered with ClinicalTrials.gov (No. NCT002226096).

Results
Among the 404 patients recruited, a total of 296 (73%) patients (151 in the intensive and 145 in the guideline groups) had all 3 CT scans (baseline, 24 and 72 hours) available for analysis (Figure 1). Hematoma volume was determined in all of these patients, but perihematomal edema volume could only be determined in 270 (67%) patients (139 in the intensive and 131 in the guideline groups) in whom CT scans were available in DICOM format. Patients with and without 3 sequential CT scans had broadly similar baseline characteristics except for median National Institutes of Health Stroke Scale score (9 with CT and 12 without CT), median Glasgow Coma Scale score (15 and 14), and mean baseline hematoma volume (12.66 and 18.42 mL). Among the 108 patients without repeat CT, 12 were dead (6 each in the guideline and intensive groups) and 14 had neurosurgical intervention (6 and 8) before the 72-hour CT.

Table 1 shows that the baseline characteristics and the median time from ICH onset to randomization of 296 patients with repeat CT scans were similar between the treatment groups. Among 296 patents with repeat CT scans, early intensive BP-lowering treatment significantly reduced BP levels during the treatment. At 1 hour, the mean systolic BP levels were 166 and 152 mm Hg, respectively (difference 11.1 mm Hg; 95% CI, 7.7 to 14.5 mm Hg; P<0.0001). During 1 to 24 hours, these levels were 157 and 145 mm Hg, respectively (difference 11.7 mm Hg; 95% CI, 8.1 to 15.3 mm Hg; P<0.0001). During 1 to 3 days, these levels were 155 and 144 mm Hg, respectively (difference 11.1 mm Hg; 95% CI, 7.7 to 14.5 mm Hg; P<0.0001).

Among 296 patients with repeat CT scans, 228 (77%; 111 in the guideline and 117 in the intensive groups) had their 24-hour CT scans undertaken within the prespecified time window, 15 (5% [8 and 7]) during 27 to 48 hours, and 53 (18% [26 and 27]) during 6 to 21 hours, and 219 patients (74% [100 and 119]) had their 72-hour CT scans undertaken within the prespecified time window, 9 (3% [7 and 2]) during 75 to 80 hours, and 68 (23% [38 and 30]) during 48 to 69 hours. Only 26 patients (9% [14 and 12]), in whom CT scans were not available in DICOM format, had their hematoma volumes analyzed using the ABC/2 method and did not have an estimation for their edema volumes. The mean initial hematoma volumes were 12.00 mL in the guideline group and 13.22 mL in the intensive group (Table 2). Compared with the guideline group, the intensive group showed significant differences of 3.15 mL (95% CI, 1.00 to 5.30 mL; P=0.004) and 2.45 mL (95% CI, 0.75 to 4.16 mL; P=0.005) less mean absolute hematoma growth at 24 and 72 hours, respectively (Table 2; Figure 2A). The mean difference in absolute

<table>
<thead>
<tr>
<th>Table 1. Baseline Characteristics by Randomized Groups</th>
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<tbody>
<tr>
<td><strong>Guideline Group</strong></td>
</tr>
<tr>
<td>----------------------</td>
</tr>
<tr>
<td>Median time from ICH onset to randomization, hours</td>
</tr>
<tr>
<td>Age, years</td>
</tr>
<tr>
<td>Male</td>
</tr>
<tr>
<td>Country of residence</td>
</tr>
<tr>
<td>China</td>
</tr>
<tr>
<td>Australia</td>
</tr>
<tr>
<td>South Korea</td>
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<tr>
<td>Medical history</td>
</tr>
<tr>
<td>Hypertension</td>
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<tr>
<td>Previous ICH</td>
</tr>
<tr>
<td>Ischemic stroke</td>
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<tr>
<td>Acute coronary event</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
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<tr>
<td>Medication</td>
</tr>
<tr>
<td>Antihypertensive therapy</td>
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<tr>
<td>Antplatelet therapy</td>
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<tr>
<td>Warfarin anticoagulation</td>
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<tr>
<td>Clinical features</td>
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<tr>
<td>Systolic BP, mm Hg</td>
</tr>
<tr>
<td>Diastolic BP, mm Hg</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
</tr>
<tr>
<td>Median NIHSS score</td>
</tr>
<tr>
<td>NIHSS score ≥14</td>
</tr>
<tr>
<td>Median GCS score</td>
</tr>
<tr>
<td>GCS score &lt;9</td>
</tr>
<tr>
<td>Location of hematoma</td>
</tr>
<tr>
<td>Lobar</td>
</tr>
<tr>
<td>Basal ganglia or thalamus</td>
</tr>
<tr>
<td>Brain stem</td>
</tr>
<tr>
<td>Cerebellum</td>
</tr>
<tr>
<td>Intraventricular extension</td>
</tr>
</tbody>
</table>

Data are n (%), mean (SD), or median (interquartile range). NIHSS indicates National Institutes of Health Stroke Scale; GCS, Glasgow Coma Scale.

increase over 72 hours was 2.80 mL (95% CI, 1.04 to 4.56 mL; P=0.002). Likewise, proportional hematoma growth was 11.9% (95% CI, 0.6% to 23.3%; P=0.04), 8.3% (95% CI, −0.7% to 17.4%; P=0.08), and 9.8% (95% CI, 1.4% to 18.2%; P=0.04) lower in the intensively managed group at 24 and 72 hours and over 72 hours, respectively (Table 2; Figure 2B). Comparable results were found when analyses were repeated without adjustment for any covariates.

Table 2 shows that the mean initial perihematomal edema volumes were 9.23 mL in the guideline group and 8.97 mL in the intensive group, respectively, and Figures 3A and 3B show no significant differences in these volumes between randomized groups over time.

Table 3 shows the frequencies of patients according to absolute increases in hematoma and edema volumes of ≥6.0, 4.0 to 5.9, 2.0 to 3.9, and ≤1.9 mL. The frequency of patients
with hematoma increase of ≥6.0 mL tended to be lower in the intensive group compared with the guideline group at 24 hours (7% versus 15%; \(P=0.06\)) and 72 hours (4% versus 12%; \(P=0.02\)). There were no clear differences in distribution of absolute growth in perihematomal edema volumes.

**Discussion**

The present analysis of the INTERACT study demonstrates that a management strategy of rapid BP lowering attenuated hematoma growth over 72 hours from the initiation of treatment compared with a more conservative policy of BP management that was based on a widely used guideline among patients who presented within several hours after ICH. In addition, there was no clear effect of the treatment on perihematomal edema. Because hematoma growth is a strong predictor of poor outcomes in ICH,15,16 these results reaffirm potential benefits of rapid physiological control of elevated BP and support the hypothesis that early intensive BP lowering may promote recovery from ICH.

Previous observational studies have demonstrated that lower BP levels early after onset of ICH is associated with reduced likelihood of hematoma growth.5,8,9 The present analysis from INTERACT supports the hypothesis generated from these studies by demonstrating that early intensive BP lowering attenuated hematoma growth in absolute terms by 3.2 mL at 24 hours in ICH. Although the Factor seven for Acute hemorrhagic Stroke Trial (FAST) failed to show any improvement in survival or functional outcome resulting from a modest reduction in hematoma growth (2.6 to 3.8 mL at 24 hours) from early use of recombinant activated Factor VII,17 this study might have been complicated by imbalances in key prognostic factors between randomized groups, comorbid effects of residual disability in older patients, and thromboembolic adverse effects.18 Thus, because the effects of treatment might not be uniform across patient subgroups,18 and the clinical benefits of any hematoma reduction obtained from BP lowering remain unclear, more data from future large-scale randomized trials are required to guide practice.

In the present analysis, beneficial effects of early intensive BP lowering on hematoma growth were likely to persist over 72 hours. However, previous studies demonstrated that hematoma growth occurred predominantly within the first

### Table 2. Effects of Early Treatment to Lower BP on Hematoma and Perihematomal Edema Growth

<table>
<thead>
<tr>
<th></th>
<th>Guideline Group</th>
<th>Intensive Group</th>
<th>Difference (95% CI)*</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Hematoma</strong></td>
<td>(n=145)</td>
<td>(n=151)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean volume, mL (SD)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>12.00 (10.89)</td>
<td>13.22 (13.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24 hours</td>
<td>15.25 (16.07)</td>
<td>13.26 (11.87)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>72 hours</td>
<td>13.41 (12.79)</td>
<td>11.94 (10.46)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adjusted mean absolute increase, mL (95% CI)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to 24 hours</td>
<td>2.40 (0.03–4.77)</td>
<td>−0.74 (−3.11–1.62)</td>
<td>3.15 (1.00–5.30)</td>
<td>0.004</td>
</tr>
<tr>
<td>Baseline to 72 hours</td>
<td>0.15 (−1.74–2.03)</td>
<td>−2.31 (−4.18–−0.43)</td>
<td>2.45 (0.75–4.16)</td>
<td>0.005</td>
</tr>
<tr>
<td>&gt;72 hours</td>
<td>1.27 (−0.43–2.98)</td>
<td>−1.53 (−3.26–0.23)</td>
<td>2.80 (1.04–4.56)</td>
<td>0.002</td>
</tr>
<tr>
<td>Adjusted mean proportional increase, % (95% CI)†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to 24 hours</td>
<td>25.8 (13.4–39.4)</td>
<td>13.6 (2.4–26.1)</td>
<td>11.9 (0.6–23.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>Baseline to 72 hours</td>
<td>6.6 (−3.5–17.7)</td>
<td>−1.7 (−11.1–8.5)</td>
<td>8.3 (−0.7–17.4)</td>
<td>0.08</td>
</tr>
<tr>
<td>&gt;72 hours</td>
<td>15.8 (3.0–30.1)</td>
<td>5.7 (−5.4–18.0)</td>
<td>9.8 (1.4–18.2)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Data are mean (SD) or adjusted mean with 95% CIs, except where indicated.

*Difference between the guideline and intensive groups.

†Because of skewed raw data, means are reported with 95% CI obtained by back transformation. Ninety-five CIs for the differences in adjusted means were calculated using the bootstrap percentile method.
several hours after ICH onset\textsuperscript{15,16} and that hematoma shrank between 24 and 72 hours probably due to clot retraction\textsuperscript{17,19}. Therefore, the effects of early treatment to lower BP on hematoma growth observed at 72 hours might be a consequence of hematoma volume reduction derived from blood pressure lowering within 24 hours.

Because perihematomal edema volume is directly related to hematoma volume\textsuperscript{20}, reduction in hematoma growth is likely to provide favorable effects on edema growth. In fact, the Recombinant Activated Factor VII ICH Trial\textsuperscript{19} and the FAST Trial\textsuperscript{17} demonstrated that recombinant activated Factor VII reduced the growth in combined volume of hematoma and edema as well as hematoma growth. However, the present analysis was unable to show any appreciable effects of early intensive BP lowering on the growth of perihematomal edema over 72 hours. The main postulated reasons for such discrepancy have been that the trial may have had been underpowered to detect potential modest effects of early intensive BP lowering on edema growth probably due to the relatively small numbers of subjects, missing data on subjects who did not have 3 sequential CT scans, and relatively low intraclass correlation coefficient for measurement of edema volume.

To our knowledge, INTERACT is the only published randomized investigation of the effects of early treatment to lower BP on hematoma and perihematomal edema growth in ICH. The key strengths include the relatively large sample size of patients included early after the onset of ICH who have had outcome assessments undertaken in a standardized and reliable manner. However, the present analysis on CT outcomes was limited to patients with repeat CT scans over a longer period of follow-up who had better clinical status (lower National Institutes of Health Stroke Scale and higher Glasgow Coma Scale scores) and smaller hematomas at baseline. The mean differences in absolute and proportional increase in hematoma volume between randomized groups over 24 hours were likely to be larger in this subgroup (3.15 mL and 11.9\%) compared with 46 patients who had only baseline and 24-hour CT (1.53 mL and 7.4\%), although these differences were not statistically significant ($P$ homogeneity = 0.48 and 0.63), and the beneficial effects of early treatment to lower BP on hematoma growth may have been overestimated in the present analysis. However, the demographic and medical history features of patients with repeat CT scans were broadly similar to those without repeat CT or in participants of other studies\textsuperscript{16,17,19} and the number of subjects who did not return to repeat CT scans due to death, neurosurgical intervention, or other causes was similar between randomized groups. We consider, therefore, that the findings reported here are reliable and broadly applicable to patients with acute ICH.
In summary, these data reaffirm potential beneficial effects of early intensive BP-lowering treatment on the growth of hematoma but not perihematomal edema over 72 hours in acute ICH. Current guidelines for the acute management of ICH provide an indication of perceived harm associated with “very high” BP levels but also highlight ongoing uncertainty over what is the optimal BP in this condition. Definitive evidence to support such a low-cost and widely applicable intervention is urgently required for ICH, because the only currently proven management strategy is stroke unit-based supportive care and rehabilitation. The main trial, INTERACT2, which aims to determine the effects of treatment on clinical outcomes in 2800 patients with ICH, started recruitment in 2008.

Sources of Funding
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Disclosures
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References

Table 3. Distribution of Absolute Growth in Hematoma and Perihematomal Edema Volumes by Randomized Groups

<table>
<thead>
<tr>
<th>Guideline Group</th>
<th>Intensive Group</th>
<th>( P ) Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute hematoma increase, mL</td>
<td>(n=145)</td>
<td>(n=151)</td>
</tr>
<tr>
<td>( \geq 6 )</td>
<td>22 (15%)</td>
<td>11 (7%)</td>
</tr>
<tr>
<td>4.0–5.9</td>
<td>6 (4%)</td>
<td>9 (6%)</td>
</tr>
<tr>
<td>2.0–3.9</td>
<td>14 (10%)</td>
<td>13 (9%)</td>
</tr>
<tr>
<td>( \leq 1.9 )</td>
<td>103 (71%)</td>
<td>118 (78%)</td>
</tr>
<tr>
<td>Absolute edema increase, mL</td>
<td>(n=131)</td>
<td>(n=139)</td>
</tr>
<tr>
<td>( \geq 6 )</td>
<td>45 (34%)</td>
<td>44 (32%)</td>
</tr>
<tr>
<td>4.0–5.9</td>
<td>20 (15%)</td>
<td>16 (12%)</td>
</tr>
<tr>
<td>2.0–3.9</td>
<td>17 (13%)</td>
<td>24 (17%)</td>
</tr>
<tr>
<td>( \leq 1.9 )</td>
<td>49 (37%)</td>
<td>55 (40%)</td>
</tr>
</tbody>
</table>

Data are n (%). Adjustments were made for hematoma location, baseline hematoma volume, and time from onset of ICH to CT scan.
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