Earlier Blood Pressure-Lowering and Greater Attenuation of Hematoma Growth in Acute Intracerebral Hemorrhage

INTERACT Pilot Phase

Hisatomi Arima, MD; Yining Huang, MD; Ji Guang Wang, MD; Emma Heeley, PhD; Candice Delcourt, MD; Mark Parsons, MD; Qiang Li, BSc; Bruce Neal, MD; John Chalmers, MD; Craig Anderson, MD; for the INTERACT Investigators*

Background and Purpose—The INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT) pilot study showed that early intensive blood pressure-lowering can attenuate hematoma growth in acute intracerebral hemorrhage. The present analysis aimed to determine the treatment effects on hematoma growth by time from intracerebral hemorrhage onset to randomization.

Methods—Patients (N=404) with acute intracerebral hemorrhage and elevated systolic blood pressure were randomly assigned to intensive or guideline-based blood pressure management. Baseline and repeat CT (24 and 72 hours) were performed and changes in hematoma volume were assessed using generalized estimating equations.

Results—Among 296 patients with all 3 CT scans available for analysis, reductions in proportional hematoma growth produced by randomized intensive blood pressure-lowering treatment over 72 hours decreased progressively with delays in initiation of study treatment: 22%, 17%, 9%, and 3% for quartile groups defined by time from onset to randomization of <2.9, 2.9 to 3.6, 3.7 to 4.8, and ≥4.9 hours, respectively (P trend=0.001). There were also smaller absolute reductions in hematoma growth with delays in initiation of study treatment (6.5 mL, 3.3 mL, 0.9 mL, and 0.6 mL), although the trend did not reach statistical significance (P trend=0.12).

Conclusions—Earlier initiation of intensive blood pressure-lowering treatment is likely to provide greater protection against hematoma growth in acute intracerebral hemorrhage.

Clinical Trial Registration Information—http://www.clinicaltrials.gov, NCT002226096.

(Stroke. 2012;43:2236-2238.)

Key Words: blood pressure-lowering ■ clinical trials ■ INTERACT ■ intracerebral hemorrhage ■ time

Hematoma growth is a strong predictor of death and dependency after intracerebral hemorrhage (ICH), and accordingly, treatment approaches to attenuate hematoma growth (eg, hemostatic treatment and intensive blood pressure [BP]-lowering) may improve prognosis in ICH. As more hematoma growth is observed in patients who present rapidly to the hospital, an earlier initiation of such treatment may provide larger protection against poor outcomes after ICH. The INTEnsive blood pressure Reduction in Acute Cerebral hemorrhage Trial (INTERACT) pilot phase demonstrated that early intensive BP-lowering reduced hematoma growth in patients with ICH. Additional information is provided here about the effects of treatment on hematoma growth by time from onset to randomization.

Methods

The design of the INTERACT study has been described in detail elsewhere. Briefly, 404 patients with CT-confirmed ICH, elevated systolic BP (150–220 mm Hg), and capacity to commence BP-lowering within 6 hours of onset were randomly assigned to an intensive lowering of BP using routine intravenous agents (target systolic BP <140 mm Hg) or guideline-based management of BP (180 mm Hg). The study protocol was approved by the ethics committee at each participating site and the procedures followed were in accordance with institutional guidelines. Written informed consent was obtained from each patient or their legal surrogate.
Outcomes for the present investigation were proportional and absolute increases in hematoma volume during the first 72 hours after ICH. Sites were required to perform CT scans according to standardized techniques at baseline and at 24/48 and 72/48 hours after the initial CT. Hematoma volume was calculated independently by 2 trained neurologists who were blind to treatment allocation (intraclass correlation coefficient for 10% CT = 0.97) using Mistar Version 3.2 (Apollo Medical Imaging Technology).

Groups of participants defined by quartiles of time from onset to randomization were used. The present subgroup analysis was not prespecified. The effects of intensive BP-lowering on hematoma growth over 72 hours were ascertained by generalized estimating equations using hematoma increases at 24 and 72 hours as repeat measures. Proportional change was log-transformed to remove skewness after addition of the value 1 to eliminate negative values, and 95% CI for the differences in adjusted means of proportional change were calculated using the bootstrap method. Comparisons of treatment effects across subgroups were performed by adding an interaction term.

**Results**

Overall, 296 patients had all 3 CT available for analyses. Patients with repeat CT scans involved fewer subjects with low Glasgow Coma Scale score and had smaller hematomas at baseline (Table I in the online-only Data Supplement). Table II in the online-only Data Supplement shows that the baseline characteristics of patients were broadly similar across quartile groups defined by time from onset to randomization. There were no significant differences between randomized groups in each subgroup except for previous ICH in the 2.9- to 3.6-hour group. The mean differences in systolic BP (mm Hg) between randomized groups during 1 to 24 hours were 14.2 (95% CI, 0.5–20.9), 6.3 (0.5–14.3), 13.5 (0.5–19.7), and 12.5 (4.4–20.6) for the quartile groups defined by time from onset to randomization of <2.9, 2.9 to 3.6, 3.7 to 4.8, and ≥4.9 hours, respectively (P trend = 0.96). Reductions in proportional hematoma growth (%) produced by more intensive BP-lowering over 72 hours decreased progressively with delays in initiation of study treatment even after adjustment for hematoma location: 22 (95% CI, 1–43), 17 (1–32), 9 (−2 to 21), and 3 (−14 to 21) for the quartile groups (Figure 1; P trend = 0.001). There were also smaller absolute reductions (mL) in hematoma growth with delays in initiation of treatment even after adjustment for location and baseline volume of hematoma: 6.5 (95% CI, 0.5–12.5), 3.3 (0.5–6.0), 0.9 (−1.0 to 2.8), and 0.6 (−1.1 to 2.3), although the trend did not reach statistical significance (Figure 2; P trend = 0.12). Similar results were obtained for crude analyses (Figures I and II in the online-only Data Supplement).

**Discussion**

The present analysis suggests that patients who receive early start of intensive BP-lowering treatment obtain a larger reduction in hematoma growth after ICH. Our findings are consistent with those obtained from the Factor seven for Acute hemorrhagic Stroke Trial (FAST), which identified greater reduction in hematoma growth in a subgroup of patients who received hemostatic therapy based on recombinant activated factor VII within 3 hours after ICH onset than those who received recombinant activated factor VII during 3 to 4 hours after onset. The FAST trial also demonstrated that favorable effects of recombinant activated factor VII on clinical outcomes were only ob-
served in patients who received treatment within 2.5 hours from onset. These findings support the hypothesis concerning a larger protection against hematoma growth and subsequent poor outcomes associated with earlier initiation of treatment after ICH.

Key strengths of INTERACT are the relatively large sample size of patients with early and rigorous evaluations made after acute ICH. However, the trial still had relatively limited power to define significant heterogeneity of treatment effects in each set of analysis. Moreover, because the present evaluation was restricted to those patients with repeat CT, who had better clinical status at baseline, the findings may not be applicable to patients with severe ICH.

Summary
The present data support the possibility that maximum beneficial effects on hematoma growth and subsequent poor clinical outcomes are likely to be obtained in those patients who receive intensive BP-lowering within the first few hours from onset of ICH.

Sources of Funding
The INTERACT study was supported by a Program Grant (358395) from the National Health and Medical Research Council. The study was designed, conducted, analyzed and interpreted by the investigators independent of sponsors.

Disclosures
None.

References
Earlier Blood Pressure-Lowering and Greater Attenuation of Hematoma Growth in Acute Intracerebral Hemorrhage: INTERACT Pilot Phase

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Earlier blood pressure lowering and greater attenuation of hematoma growth in acute intracerebral hemorrhage: INTERACT pilot phase

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Cover title: BP lowering and hematoma growth by time
## Supplemental Table S1. Baseline characteristics of subjects with and without repeat CT scans over 72 hours

<table>
<thead>
<tr>
<th></th>
<th>Subjects with repeat CT</th>
<th>Subjects without repeat CT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 296)</td>
<td>(n = 108)</td>
</tr>
<tr>
<td>Median time from ICH onset to randomization (hours)</td>
<td>3.67 (2.85-4.85)</td>
<td>3.64 (2.97-4.65)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 (12)</td>
<td>61 (14)</td>
</tr>
<tr>
<td>Male</td>
<td>64</td>
<td>67</td>
</tr>
<tr>
<td>Asian</td>
<td>96</td>
<td>99</td>
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<tr>
<td>Medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>74</td>
<td>76</td>
</tr>
<tr>
<td>Previous ICH</td>
<td>12</td>
<td>10</td>
</tr>
<tr>
<td>Medication</td>
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<tr>
<td>Antihypertensive therapy</td>
<td>43</td>
<td>44</td>
</tr>
<tr>
<td>Antiplatelet therapy</td>
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<td>7</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Clinical features</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>181 (18)</td>
<td>180 (18)</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>102 (14)</td>
<td>105 (16)</td>
</tr>
<tr>
<td>NIHSS score ≥14</td>
<td>28</td>
<td>38</td>
</tr>
<tr>
<td>GCS score &lt; 9</td>
<td>7</td>
<td>13 *</td>
</tr>
<tr>
<td>Baseline hematoma volume (ml)</td>
<td>9.0 (4.4-16.2)</td>
<td>11.1 (7.5-25.3)*</td>
</tr>
<tr>
<td>Lobar location of hematoma</td>
<td>8</td>
<td>10</td>
</tr>
</tbody>
</table>

Data are %, mean (SD), or median (IQR).
ICH denotes intracerebral hemorrhage, BP blood pressure, NIHSS National Institutes of Health Stroke Scale, GCS Glasgow Coma Scale.

*P<0.05 versus subjects with repeat CT based on a Wilcoxon test or a chi-square test.
**Supplemental Table S2. Baseline characteristics by time from onset to randomization**

<table>
<thead>
<tr>
<th>Time from onset to randomization</th>
<th>&lt;2.9h</th>
<th>2.9-3.6h</th>
<th>3.7-4.8h</th>
<th>≥4.9h</th>
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</thead>
<tbody>
<tr>
<td><strong>Intensive (n=40)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 (12)</td>
<td>65 (11)</td>
<td>63 (11)</td>
<td>63 (12)</td>
</tr>
<tr>
<td>Male</td>
<td>60</td>
<td>47</td>
<td>62</td>
<td>65</td>
</tr>
<tr>
<td>Asian</td>
<td>98</td>
<td>100</td>
<td>95</td>
<td>91</td>
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<tr>
<td><strong>Guideline (n=34)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>63 (14)</td>
<td>62 (14)</td>
<td>61 (13)</td>
<td>62 (11)</td>
</tr>
<tr>
<td>Male</td>
<td>71</td>
<td>67</td>
<td>71</td>
<td>73</td>
</tr>
<tr>
<td>Asian</td>
<td>88</td>
<td>94</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

**Medical history**

- Hypertension: 80 79 76 78 72 71 62 70
- Previous ICH: 15 15 21 3 * 5 6 12 18

**Medication**

- Antihypertensive therapy: 48 41 50 53 33 43 29 45
- Antiplatelet therapy: 8 12 13 6 10 3 9 5
- Warfarin: 0 3 0 0 3 0 3 0

**Clinical features**

- Systolic BP (mmHg): 180 (19) 180 (18) 182 (18) 183 (18) 179 (17) 183 (20) 180 (19) 180 (18)
- Diastolic BP (mmHg): 100 (13) 105 (13) 102 (14) 104 (13) 100 (14) 104 (17) 99 (14) 104 (12)
- NIHSS score<14: 20 24 26 33 33 37 26 28
- GCS score<9: 5 9 3 6 10 9 9 5
- Baseline hematoma volume (ml): 9.6 (6.0-14.6) 7.8 (3.0-13.9) 7.3 (3.6-11.7) 11.1 (5.4-16.7) 6.5 (2.8-8.9) 8.5 (4.4-13.4) 7.4 (1.3-7.4) 9.1 (3.6-14.5)
- Lobar location of hematoma: 5 6 8 8 8 3 9 18

Data are %, mean (SD), or median (IQR). ICH denotes intracerebral hemorrhage, BP blood pressure, NIHSS National Institutes of Health Stroke Scale, GCS Glasgow Coma Scale.

*P<0.05 between randomized groups based on a Wilcoxon test or a chi-square test.
Supplemental Figure S1. Unadjusted effects of early treatment to lower blood pressure on proportional increase in hematoma volume over 72 hours by time from onset to randomization
Solid boxes represent estimates of treatment effects; areas of the boxes are proportional to the reciprocal of the variance of the estimates. Horizontal lines represent 95% CI.
### Supplemental Figure S2. Unadjusted effects of early treatment to lower blood pressure on absolute increase in hematoma volume over 72 hours by time from onset to randomization

Conventions as for Supplemental Figure S1.
急性期脳内出血における早期降圧と血腫増大の抑制：
INTERACT パイロットフェーズ

Earlier Blood Pressure-Lowering and Greater Attenuation of Hematoma Growth in Acute Intracerebral Hemorrhage
INTERACT Pilot Phase

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背景および目的：INTERACT パイロット試験で、急性期脳内出血においては早期の強化降圧により血腫増大を抑制できることが示された。本解析の目的は、脳内出血の発症から無作為割り付けまでの時間により血腫増大に対する治療効果を判定することである。

方法：急性期脳内出血および収縮期血圧上昇に有する患者（N = 404）を、強化降圧管理またはガイドラインに基づく降圧管理に無作為に割り付けた。ベースライン時 CT および反復 CT (24 時間および 72 時間) 行い、一般化された推定方程式を用いて血腫量の変化を評価した。

結果：3 回の CT スキャンをすべて解析に使用可能な 296 例の患者において、無作為割り付けされた強化降圧治療による 72 時間よりももたらされた血腫増大率の低下は、試験治療の開始の遅延とともに徐々に減少した：発症から無作為割り付けまでの時間で 2.9 時間、2.9 ～ 3.6 時間、3.7 ～ 4.8 時間、および 4.9 時間以下、定義される血腫増大の範囲に含まれるそれぞれで 22%、17%、9%、および 3% (傾向の p 値 = 0.001)。また、試験治療の開始の遅延とともに血腫増大の絶対的減少を小さくなったが (6.5 mL, 3.3 mL, 0.9 mL, および 0.6 mL)、傾向は統計学的有意性に達しなかった (傾向の p 値 = 0.12)。

削減：急性期脳内出血においては、強化降圧治療の開始が早いと血腫増大の予防効果が高くなる傾向が強い。


<table>
<thead>
<tr>
<th>発症から無作為割り付けまでの時間</th>
<th>増大率</th>
<th>強化降圧管理</th>
<th>ガイドライン管理</th>
<th>増大率の差 (%)</th>
<th>傾向の p 値</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤2.9 時間</td>
<td>-7%</td>
<td>16%</td>
<td></td>
<td>22% (1 ～ 43)</td>
<td>0.001</td>
</tr>
<tr>
<td>2.9 ～ 3.6 時間</td>
<td>20%</td>
<td>37%</td>
<td></td>
<td>9% (1 ～ 32)</td>
<td></td>
</tr>
<tr>
<td>3.7 ～ 4.8 時間</td>
<td>4%</td>
<td>5%</td>
<td></td>
<td>3% (1 ～ 14)</td>
<td></td>
</tr>
<tr>
<td>≥4.9 時間</td>
<td>22%</td>
<td>25%</td>
<td></td>
<td>5% (1 ～ 21)</td>
<td></td>
</tr>
</tbody>
</table>

発症から無作為割り付けまでの時間別にみた、早期の降圧治療が 72 時間の血腫増大率に及ぼす影響、結果は血腫の位置について補正した。

発症から無作為割り付けまでの時間別にみた、早期の降圧治療が 72 時間の血腫増大率の絶対増大値について、絶対値の差が 0.5 mL 以上と有意差を認めたもの。

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