Early intensive blood pressure lowering in intracerebral hemorrhage attenuated hematoma growth over 72 hours, but the effect on clinical outcome remains unclear

**Clinical Problem:** A 70 year old, previously healthy man is admitted to hospital with an acute spontaneous intracerebral hemorrhage (ICH). The onset was 1 hour ago, his Glasgow Coma Scale (GCS) score is 14 and his blood pressure is 190/105.

**Clinical Question:** In patients with CT confirmed intracerebral hemorrhage and elevated systolic blood pressure (150-220mmHg), does intensive blood pressure lowering (to a target systolic BP of 140mmHg) vs. standard of care (target systolic blood pressure of 180mmHg) within 6 hours of onset affect hematoma and perihematomal edema volumes over 72 hours?

**Search Strategy:**
Cochrane database search yielded no relevant systematic reviews.
Pubmed search using the terms “intracerebral hemorrhage” OR “hemorrhagic stroke” AND “blood pressure”, limited to humans, English language, adults (18+), and meta-analysis, yielded no relevant results.
Pubmed search with the same terms, but limited to randomized-controlled trials, published in the last 10 years gave 56 results. The above search terms AND “acute lowering” yielded 9 articles: 5 were related to INTERACT, 1 was an herbal medicine study, 2 were small studies, and 1 was a trial using oral candesartan to reduce blood pressure in ischemic and hemorrhagic stroke over 7 days.
INTERACT with chosen because it was the largest study evaluating acute lowering of blood pressure after intracerebral hemorrhage.

**Clinical Bottom Lines:**
1. Rapid blood pressure lowering (to target sBP 140mmHg) within 6 hours of spontaneous intracerebral hemorrhage attenuates hematoma growth over 72 hours (difference of 2.80mL 95% CI 1.04-4.54).¹
2. There were no significant differences in clinical outcomes at 90 days.²

**The Evidence:** INTERACT is a multicentre, open, blinded outcome, randomized trial. There were 404 patients recruited, with 296 having requisite CT scans available for analysis (baseline, 24h, 72h).
**Inclusion criteria:** age ≥ 18 with CT confirmed spontaneous intracerebral hemorrhage and elevated systolic blood pressure (≥ 2 measurements of ≥ 150mmHg and ≤ 220mmHg), and capacity to start treatment within 6 hours of ICH.
**Exclusion criteria:** clear indication or contraindication to intensive blood pressure lowering, ICH secondary to structural cerebral anatomy or the use of a thrombolytic agent, recent ischemic stroke, deep coma, significant pre-stroke disability or medical illness, and early planned neurological intervention
Patients were randomly assigned to intensive BP lowering strategy (goal SBP of 140mmHg within 1 hour of randomization, for 7 days) or Best Practice Standard as outlined by American Heart Association guidelines 1999 (goal SBP of 180mmHg).³
Outcomes: Primary outcomes were absolute and proportional increases in hematoma and perihematomal edema volumes during the first 72 hours after ICH. Volumes were calculated by 2 independent neurologists blind to clinical data and date of scan. The main clinical endpoints were death and dependency (mRS score 3-5) at 90 days. Other measured clinical outcomes were National Institutes of Health Stroke Scale (NIHSS), modified Rankin Scale (mRS), Barthel Index, EuroQol 5D (EQ5D).

Data:

Primary Outcomes

<table>
<thead>
<tr>
<th>Hematoma (adjusted mean absolute increase, mL)</th>
<th>Guideline Group</th>
<th>Intensive Group</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Guideline (Standard Care) Group</td>
<td>-</td>
<td>-</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline to 24h</td>
<td>2.40 (0.03-4.72)</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 72h</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;72h</td>
<td>1.27 (-0.43-2.98)</td>
<td>-1.53 (-3.28-0.25)</td>
<td>2.80 (1.04-4.56)</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Effect On Peri-Hematomal Edema: There was no significant change in peri-hematomal edema between Standard Care and Treatment groups.

Other outcomes

Mean systolic Blood Pressure at various times

<table>
<thead>
<tr>
<th>Time from onset</th>
<th>Guideline Group</th>
<th>Intensive Group</th>
<th>Difference</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1hr</td>
<td>166</td>
<td>152</td>
<td>13.7 (8.5-18.8)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1-24hr</td>
<td>157</td>
<td>145</td>
<td>11.7 (8.1-15.3)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Day1-3</td>
<td>155</td>
<td>144</td>
<td>11.1 (7.7-14.5)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Clinical Endpoints of Death, Dependency, mRS Score, NIHSS, medical Barthel Index Score, median MMSE, median EQ5D: There was no significant difference in any clinical outcomes between the Standard Care and Treatment group at 90 days.

Comments:
1. Clinical significance: Despite positive findings of attenuated hematoma growth, there were no significant differences in death, dependency or any measured clinical scales.
2. Methods: Most commonly used intravenous blood pressure reducing agents were frusemide, urapidil, phentolamine, and glyceryl trinitrate. These agents are not popular choices in North America, and may directly affect hematoma size, outside of their blood pressure lowering effect (expert opinion).
3. External validity: There were only 404 patients in this trial. However, in the larger Scandinavian candesartan acute stroke (SCAST) in which oral candesartan was given to patients with acute stroke and elevated blood pressure (which was gradually lowered over 7 days), subgroup analysis revealed similar results to INTERACT. Specifically, in the 14% (N=274) of participants with hemorrhagic stroke, there was no statistical difference in composite vascular endpoint or functional outcome between candesartan versus placebo group.4
4. Future Directions: The next phase of this study, INTERACT 2, will test if a strategy of early intensive blood pressure lowering compared to conservative blood pressure lowering in patients with
elevated blood pressure within 6 hours of acute intracerebral hemorrhage improves the outcome of death or disability at 3 months after onset.⁵

References:


Key Words: hemorrhagic stroke, intracerebral hemorrhage, blood pressure, hematoma, perihematomal edema, hypertension, acute lowering

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