Update on Hemorrhagic Stroke

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Recent Advances in Neurology
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Nothing to disclose

Some slides courtesy of Dr. Claude Hemphill

Frequency of Stroke by Subtype

- Ischemic: 84%
  - Thrombotic: 53%
  - Embolic: 11%
- Hemorrhagic: 16%
  - Intracerebral: 10%
  - Subarachnoid: 6%

High Burden of Disease

- High morbidity and mortality
  - 35-52% 30-day mortality
  - 20% of ICH patients independent at 6 mo
- 34% of years of potential life lost to stroke
- Lifetime cost per case ~ $124,000
- Total lifetime cost for annual US cases >$4B

- 5-10% of all strokes
- Incidence: 6-16 per 100,000/ year
- Aggregate costs of $5 billion/ year
- One-third of potential years of life lost before age 65 due to stroke

Taylor et al. Stroke 26:1459-1466, 1996

Highlights for ICH

- Predictors of outcome: The ICH Score
- Treatment for re-hemorrhage: Factor VIIa
- Surgical treatment
- Blood pressure management
Predictors of mortality in ICH

- GCS on admission
- Hematoma size (ICH volume)
- Blood pressure (pulse pressure)
- Intraventricular blood
- Hematoma enlargement
- Age

Broderick et al. Stroke 24:987-993, 1993

Determination of the ICH Score

<table>
<thead>
<tr>
<th>Component</th>
<th>ICH Score Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>GCS Score</td>
<td></td>
</tr>
<tr>
<td>3-4</td>
<td>2</td>
</tr>
<tr>
<td>5-12</td>
<td>1</td>
</tr>
<tr>
<td>13-15</td>
<td>0</td>
</tr>
<tr>
<td>ICH Volume (cc)</td>
<td></td>
</tr>
<tr>
<td>≥ 30</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 30</td>
<td>0</td>
</tr>
<tr>
<td>Intraventricular Hemorrhage</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Infratentorial Origin</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1</td>
</tr>
<tr>
<td>No</td>
<td>0</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>≥ 80</td>
<td>1</td>
</tr>
<tr>
<td>&lt; 80</td>
<td>0</td>
</tr>
</tbody>
</table>

Total ICH Score 0 - 6

ICH Volume

Select CT slice with largest ICH
A = longest axis (cm)
B = longest axis perpendicular to A (cm)
C = # of slices x slice thickness (cm)

Estimated volume of spheroid
Correlates well w/ planimetric CT analysis

Hemphill, Stroke 2001
**Rehemorrhage in ICH**

- Initial CT
- 10 hours later

**Recombinant Factor VIIa**

- Decrease hematoma expansion in ICH?
- Initial trial: 48 pt dose escalation safety study; w/in 4 hours of onset
- No increase in thrombotic complications or edema
- 17% 1 hour hematoma enlargement (19% at 24 hours)
- FAST trial for mortality and functional outcome


**Modified Rankin Scale at Day 90**

- 160 µg/kg
- 80 µg/kg
- 40 µg/kg
- Placebo

FAST Trial

Efficacy and Safety of Recombinant Activated Factor VII for Acute Intracerebral Hemorrhage


Factor VII: Survival and Outcome in ICH


Surgical Trial for ICH (STICH)

- Completed in 2003
- Largest study of surgery in ICH (>1000 pts)
- Does a policy of “Early Surgery” improve outcome in patients with spontaneous supratentorial ICH compared with a policy of “Initial Conservative Treatment”?  
  - Randomisation within 72 hours of ictus  
  - Surgery within 24 hours of randomisation

STICH - Results

<table>
<thead>
<tr>
<th>Mortality</th>
<th>Early Surgery</th>
<th>Initial Conservative tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alive</td>
<td>304 (64%)</td>
<td>316 (63%)</td>
</tr>
<tr>
<td>Dead</td>
<td>173 (36%)</td>
<td>189 (37%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Primary Outcome (“Prognosis based” functional outcome)</th>
<th>Early Surgery</th>
<th>Initial Conservative tx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Favourable</td>
<td>112 (26%)</td>
<td>118 (24%)</td>
</tr>
<tr>
<td>Unfavourable</td>
<td>346 (74%)</td>
<td>351 (76%)</td>
</tr>
</tbody>
</table>

P = 0.71  
P = 0.41

- No Difference
  - 26% of patients randomised to Initial Conservative Treatment later had surgery
  - Early surgery is not harmful
  - There is no evidence favoring early surgery in supratentorial ICH

Mendelow et al. Lancet January 29, 2005
BP in ICH - Expert Consensus

- SBP >200 mmHg or MAP >150 mmHg
  - Consider aggressive reduction in blood pressure
- SBP >180 mmHg or MAP >130 mmHg
  - With suspicion for elevated ICP should consider ICP monitoring and target CPP >60-80 mmHg
- Without concern for ICP, MAP <110 (BP 160/90)
  - With close monitoring
  - Maintain MAP < 130 mm Hg (~180/110), in patients with a h/o hypertension
  - MAP < 100 mmHg post-op (if surgical evacuation)
  - Keep SBP > 90 mmHg

Arbitrary expert opinion based on balancing concerns of rehemorrhage and perihematoma ischemia

BP lowering: how to do it

- Labetalol
  - 5-10 mg IV bolus every 10-15 minutes
  - Infusion, begin at 5 mg/hr and titrate
- Nitroprusside
  - Infusion, start at 2 μg/kg/min and titrate
  - Theoretical issues of increase in ICP (not a big deal)
- Nicardipine
  - We don’t bolus
  - Start IV infusion at 2.5 mg/hr and titrate up by 0.5 mg/hr increments
  - We use central lines for prolonged usage

AHA ICH Guidelines

**TABLE 2. Suggested Recommended Guidelines for Treating Elevated Blood Pressure in Spontaneous ICH**

1. If SBP is >200 mmHg or MAP is >150 mmHg, then consider aggressive reduction of blood pressure with continuous intravenous infusion, with frequent blood pressure monitoring every 5 minutes.
2. If SBP is >160 mmHg or MAP is >100 mmHg and there is evidence of exacerbation of elevated ICP, then consider monitoring ICP and reducing blood pressure using intermittent or continuous intravenous medications to keep cerebral perfusion pressure >60 to 80 mm Hg.
3. If SBP is >160 mmHg or MAP is >100 mmHg and there is no evidence of exacerbation of elevated ICP, then consider a modest reduction of blood pressure, i.e., MAP of 100 mmHg or larger blood pressure of 130/90 mmHg using intermittent or continuous intravenous medications to control blood pressure, and closely reexamine the patient every 15 minutes.

BP indicators: systolic blood pressure; MAP, mean arterial pressure

Blood pressure trials: ATACH

- ATACH: Antihypertensive Treatment in Acute Cerebral Hemorrhage
- NIH sponsored pilot study in 60 patients
- "Dose-escalation" study of feasibility of achieving 3 successive BP goals for 24 hours after acute ICH
- Safety evaluation by decline in GCS of 2 points or NIHSS of 4 points
- Results: Early BP reduction within 3 hours was well-tolerated; no significant difference in outcomes in the treatment groups.
Blood pressure trials: INTERACT

- INTERACT: Intensive Blood Pressure Reduction in Acute Cerebral Hemorrhage
- 404 patients treated within 6 hours of onset
- Intensive group: SBP goal 140 mmHg (n=203) vs. Standard group; SBP 180 mmHg (n=201)
- Outcomes: hematoma volume at 24 hours; 90 day safety and clinical outcomes
- Results: RR 36% lower hematoma growth in intensive group; ARR 8% (CI 1.0-17%, p=0.05)


ICH Guidelines

Guidelines for the Management of Spontaneous Intracerebral Hemorrhage in Adults: 2007 Update: A Guideline From the American Heart Association/American Stroke Association Stroke Council, High Blood Pressure Research Council, and the Quality of Care and Outcomes in Research Interdisciplinary Working Group. The American Academy of Neurology affirms the value of this guideline as an educational tool for neurologists.

Joseph Broderick, Snyder Connolly, Edward Feldman, Daniel Hasley, Carlos Kase, Derek Krieger, Marc Mayberg, Lewis Morgenstern, Christopher S. Ogilvy, Paul Vescia and Mario Zuccarello


DOI: 10.1161/STROKEAHA.107.183689

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Highlights for SAH

- Detection and screening
- Misdiagnosis
- Outcomes
- Medical complications
Aneurysm Detection

• Most detected incidentally by imaging
• Majority are asymptomatic, unruptured
• Only 6% per year with symptoms
  – Headache (focal or generalized)
  – Cranial nerves (dilated pupil, diplopia, vision loss, dysarthria)
  – Brain stem (weakness, numbness, dizziness)
• Aneurysm rupture may be first symptom

Aneurysm Screening

• General screening not recommended or cost-effective, but remains controversial
• Exceptions in high risk genetic or rare familial conditions
  – Polycystic kidney disease
  – Family history of two first-degree relatives
• Cerebral angiogram gold standard
• Newer imaging modalities
  – CTA
  – MRA

Misdiagnosis of SAH

• Common misdiagnosis: 32% pooled analysis
  – Failure to appreciate the spectrum of clinical symptoms
  – Failure to understand limitations of CT
  – Failure to perform/interpret lumbar puncture
• Leads to delay in diagnosis (mean 6 days) and worse outcomes compared to correct diagnosis
• Greater than 2 weeks from onset makes interpretation of tests difficult

Outcomes

• Case fatality remains high >50% at discharge, and 30day mortality of 45%
• Mod-severe disability among 30% of survivors requiring long-term care
• Among good outcomes, high incidence of cognitive dysfunction, mood disorder
• Clinical grade, amount of blood, age predict outcome

Edlow and Caplan, NEJM 342(1) 2000
Proportion of patients with in-hospital death (solid bar) or adverse outcomes (stippled bar) by hospital treatment volume quartile. Rates of adverse outcome and mortality were different in the volume quartiles (P=0.001). Adverse outcomes were defined as in-hospital death or discharge to a nursing home or rehabilitation facility.

Stroke. 2002;33:1851-1856

Medical complications are common

- Life-threatening complications occur in up to 40% of SAH patients
- Contributes to 23% of overall mortality

Cardiac arrhythmia 30%
Pulmonary edema 23%
Hepatic dysfunction 20%
Renal failure 7%

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Why does it matter?

- Contributes to morbidity and mortality
- Complicates management of neurological complications
- Impacts quality of patient care; length of stay and cost of care

Figure 1: Outcomes after SAH

- Fever, hyperglycemia and anemia requiring transfusion were most associated poor neurological outcomes (mRS>2)
- Cardiac complications are common, but mostly benign.
- Troponin leak and cardiac dysfunction have been associated with worse outcome
Cardiac complications

- Sympathetic stimulation induces catecholamine release in the myocardium
- Leads to impaired systolic and diastolic function, repolarization abnormalities, and myocardial damage
- Definite causal relationship with worse vasospasm and neurological outcome remains unclear

*Van del Bilt, et al. Neurology 2009*

Fever Management

- Growing evidence that fever is associated with poor neurological outcomes
- 25% from non-infectious etiologies
- Small studies of safety of aggressive fever control
- Significant practice variability

Glucose control

- Hyperglycemia is associated with worse outcomes
- Aggressive treatment of hypoglycemia after SAH generally beneficial in subgroup analyses
- Limited safety data on insulin infusion
  - Microdialysis studies showing cerebral hypoglycemia
  - Target serum glucose <140 mg/dl

*The NEW ENGLAND JOURNAL of MEDICINE
Intensive versus Conventional Glucose Control in Critically Ill Patients
You K, Greer N, tight management*

Optimal Hgb/Hct?

- Anemia requiring transfusion associated with worse outcome
- Hemodilution advocated for vasospasm
  - Target Hct 30% to optimize O2 delivery and blood viscosity
  - New measures of PbtO2 and microdialysis suggest cerebral hypoxia at these levels
Hyponatremia

- Occurs 1/3 of patients
- Associated with hypovolemia in cerebral salt wasting
- SIADH less common
- Complex interplay of neurohormonal effects
  - hyperreninemic hypoaldosterone syndrome

Conclusions

- General aneurysm screening is not recommended
- Misdiagnosis of SAH occurs commonly
- Medical complications have a significant burden on outcomes after SAH
- Majority of evidence is from observational studies; need for clinical trial level data
- Future challenge is to incorporate emerging evidence and new technologies to improve our understanding and refine current management strategies

SAH Guidelines

Guidelines for the Management of Aneurysmal Subarachnoid Hemorrhage. A Statement for Healthcare Professionals From a Special Writing Group of the Stroke Council, American Heart Association
Stroke published online Jan 22, 2009;
DOI: 10.1161/STROKEAHA.108.191395