Controversies in Hemorrhagic Stroke Management

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Disclosures

• AHA/ASA
Outline

- Blood pressure
- VTE
- Coagulopathy
- Early mobilization
- Systems of care
ICH Epidemiology

• 15% of stroke in North America
• Shifting populations
  – 80% increase in ICH in people 75 years and older
  – 50% decrease in ICH in people under 60 years of age
  – Suggest improved blood pressure control decreasing hypertensive bleeds
  – Increased cerebral amyloid angiopathy + use of antithrombotic medication in elder population
ICH Outcome and Prognosis

• No significant improvement over past decade
• 30 day mortality rate 40%
  – Less than 50% of survivors independent at 1 year
• 1/3 patients experience hematoma expansion within first 24 hours
• Initial hematoma size strong predictor of outcome
• Location matters
  – Improved survival with lobar hemorrhages compared to deep, regardless of size
SAH Epidemiology & Prognosis

- 3-5% of strokes
- 30,000 individuals in the US annually
  - Possibly underestimated
- Despite continued advances
  - Mortality approaches 50%
  - <60% of survivors independent
Controversy 1: Blood Pressure

- 75% of patients with ICH present with BP > 140/90
  - Pre-stroke hypertension a significant risk factor for ICH
  - BP markedly elevates during ICH event
    - Damage to autonomic nervous system
    - Activation of the neuroendocrine system
      - Sympathetic activation
      - Renin-angiotensin system
      - Glucocorticoid system
    - Distress from headache
      - Often spontaneously declines over first several days
• Association between higher early BP and higher mortality
• Mechanism of increased BP may be related to cerebral autoregulation
• Concern for acute lowering of BP (old paradigm)
  – Concern for inducing perihematomal ischemia
  – Perpetuation of elevated ICP
**Table 1. Summary of recommendations for BP management in acute ICH from international guidelines**

<table>
<thead>
<tr>
<th>Guidelines</th>
<th>BP level, mm Hg</th>
<th>Recommended action</th>
<th>Monitoring</th>
</tr>
</thead>
<tbody>
<tr>
<td>American Heart Association/American Stroke Association (2007 and 2010) [24, 25]</td>
<td>SBP &gt;200 or MAP &gt;150</td>
<td>Consider aggressive BP reduction with IV agents</td>
<td>Monitor BP every 5 min</td>
</tr>
<tr>
<td></td>
<td>SBP &gt;180 or MAP &gt;150 and suspicion of elevated ICP</td>
<td>Consider monitoring ICP and reducing BP with IV medication</td>
<td>Maintain a cerebral perfusion pressure of &gt;60–80 mm Hg</td>
</tr>
<tr>
<td></td>
<td>SBP &gt;180 or MAP &gt;130 with no suspicion of elevated ICP</td>
<td>Consider a modest reduction of BP, e.g., a target BP of 160/90 mm Hg</td>
<td>Monitor BP every 15 min</td>
</tr>
<tr>
<td>European Stroke Organisation (2014) [23]</td>
<td>Within 6 h of ICH onset, intense BP reduction to a target of &lt;140 mm Hg systolic within 1 h is safe and may be superior to a target of &lt;180 mm Hg. No specific agent can be recommended. The strength of this recommendation is weak and is based on evidence of moderate* quality.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

BP = Blood pressure; SBP = systolic blood pressure; MAP = mean arterial blood pressure; ICP = intracranial pressure; ICH = intracerebral haemorrhage; IV = intravenous.

* Moderate-quality evidence described as evidence for which ‘further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate’.
• Safety of acute blood pressure lowering - CTP Data
  – CT perfusion data does not demonstrate perihematomal ischemia with acute BP lowering
  – No relationship between BP change and perihematomal cerebral blood flow
  – No relationship between BP lowering and perihematomal edema expansion
New Evidence

• INTERACT trial
  – 404 patients, enrolled within 6 hours of ICH onset
  – Stepped BP lowering protocol
    • 140mmHg intensive lowering group
    • 180mmHg guideline group
  – Outcomes
    • Early intensive BP lowering was safe
    • Trend towards minimized hematoma growth in patients in intensive lowering group
• INTERACT 2
  – 2839 patients enrolled within 6 hours of ICH
  – Stepped BP lowering protocol using IV and oral agents
    • 140mmHg intensive lowering group
    • 180mmHg guideline group
  – Intensive lowering of BP safe
  – Did not result in significant reduction in death or severe disability
  – mRS scores trended towards improved functional outcomes with intensive BP lowering
Controversy 1: Blood Pressure

- 2015 AHA/ASA guidelines
  - For patients with SBP between 150-220mmHg & without contraindication to acute BP treatment, lowering of SBP acutely to < 140mmHg is safe and may improve functional outcome
New Evidence

• ATACH trial
  – 60 patients enrolled within 6 hours
  – IV nicardipine used to target 3 treatment tiers for 18-24 hours
    • 170-220mmHg
    • 140-170mmHg
    • 110-140 mmHg
  – BP lowering safe and well tolerated
  – No increased safety events at lower BP
New Evidence

• **ATACH II Trial**
  – Enrolled GCS > 5, hematoma volume < 60cm³, SBP>180mmHg
  – Targeted BP ranges of 140-179mmHg or 110-139mmHg
  – Stopped early for futility
  – No difference in death or disability at 90 days

• **Future directions**
  – Next target
  – SBP variability during first 24 hours may be more significant than maximum SBP
Controversy 2: VTE Prophylaxis

- VTE in ICH & SAH
  - Likely under-reported
  - Symptomatic versus asymptomatic
  - Retrospective review of all stroke types
    - Symptomatic ICH 1.93% in ICH, 1.17% in ischemic stroke
  - Other reviews suggest prevalence up to 2.9%
  - ICH associated with 4x higher risk of future DVT than ischemic stroke
The Concern: Expansion

2.0 hours after onset

6.5 hours after onset
Risk for Hematoma Expansion

- Short time from sx onset to first CT
- Large hematoma size
- Irregular hematoma shape, heterogeneous hemorrhage
- Elevated BP
- Initial GCS score < 8, high NIHSS
- History of cerebral infarction
- White matter hyperintensities on MRI
- Increased Sr Cr

- Liver disease
- Hyperglycemia – acute or chronic
- Hypo or hypercholesterolemia
- ETOH consumption
- Low or high fibrinogen level
- Body temp > 37.5C
- IVH
- Oral anticoagulation, elevated INR
- Use of antithrombotic prior to hemorrhage
Options for VTE Prophylaxis

- Unfractionated & low molecular weight heparin
  - No RCT in hemorrhagic stroke
  - No studies comparing UF & LMWH in hemorrhage
  - Systematic review and meta-analysis
    - UF & LMW heparin within 48-72 hours of stable hematoma
    - Significant reduction in the rate of PE (1.7% vs 2.9%; P=0.01)
    - No significant effect on the rate of DCT
    - No increased mortality rate
    - No increase in hematoma size
Options for VTE Prophylaxis

• Mechanical prophylaxis
  – Not studied in hemorrhagic stroke specifically, mixed studies
  – IPC significantly decreases the rate of DVT and 30-day fatality rate in mixed stroke studies
  – Graduated compression stockings: mixed stroke, multi-centered RCT showed no benefit and a higher rate of skin complications
Controversy 3: Coagulopathy

• NOAC vs. DOAC – words matter!
• Warfarin versus non-vitamin K antagonist oral anticoagulants (DOAC)
  – 30-50% less likely to experience ICH on noac
  – Hematoma may be smaller and less likely to expand
• Warfarin associated ICH with elevated INR
  – FFP and vitamin K
  – Prothrombin complex concentrates (3 & 4 factor)
  – Factor VII
Reversal of Coagulopathy

- Antiplatelets for patients on antithrombotics
- DOAC reversal agents in development and/or approved
- Other options
  - PCC
  - Activated charcoal if taken recently
  - Hemodialysis
Controversy 4: Mobilization

- General consensus regarding early rehabilitation
- Association with outcome
- Questions remained:
  - How early is early?
  - What does mobilization mean?
  - Data to support intervention with improve outcomes?
- AVERT Trial
  - Randomized controlled trial, single blinded
  - Multicenter, international; 56 stroke units in 5 countries
    - Australia, New Zealand, Europe, Asia
AVERT Trial

- Patients enrolled (2006-2014) (Bernhardt et al., 2015)
  - > 18, ischemic stroke or ICH, +/- tPA
  - Excluded patients with previous disability (mRS>2), early deterioration, ICU admission, palliative treatment, unstable coronary condition, SBP < 110mmHg or > 220mmHG, SPO2<92%, HR <40 or >110, temp > 38.5C, SAH

- 1:1 randomization, usual stroke unit care or early mobilization + standard stroke unit care

- Very early mobilization
  - Within 24 hours
  - Included sitting, standing & walking
  - At least 3 OOB sessions
AVERT Trial

- Outcomes measured
  - mRS at 3 months (goal 0-2)
  - Time to walking 50m
  - Unassisted walking at 3 months
  - Complications

- Results
  - 1054 VEM, 1050 usual care
  - Similar groups
  - Mean time to randomization 18 hours
    - VEM group mobilized by 18.5 hours after stroke, more frequent OOB sessions
    - Usual care group mobilized by 22.4 hours after stroke
  - More pts in the usual care group had favorable outcome than VEM group by 3 months
  - No difference in non-fatal adverse events or mortality
AVERT Trial

• Why worse outcomes?
  – Worsened brain injury?
  – Period of plasticity after stroke?
  – Study characteristics?

• Critiques of the study
  – mRS may not be the best tool to assess recovery
  – Small window of time between VEM and usual group
  – Decreasing time to mobilization for usual group as study progressed
  – Large strokes/hemorrhages excluded
AVERT: Digging Deeper

• Usual care
  – Still early by many organization’s standards
  – Evaluating all patients (VEM & usual care) for trends (Berhardt, 2016)

• Assessing ‘dose’ of activity
  – Younger patients & low NIHSS (<7.5) high probability of favorable outcome
  – Short, frequent OOB activity associated with favorable outcomes at 3 months
  – Increasing the number of minutes out of bed associated with worse outcomes at 3 months
• What AVERT should NOT tell us
  – Immobility for prolonged period of time

• Immobility after stroke associate with
  – Muscle wasting
  – Neuronal changes from disuse

• What AVERT does tell us
  – Caution when mobilizing patients in the first 24 hours post stroke
    • Prolonged periods out of bed
  – Additional research is needed to understand who, when and how much
• How should ICH & SAH be handled by
  – ASRH, PSC, CSC stroke programs
  – If transferred, when?
  – If diversion protocol, when and how?
    • Lack of stroke scales to help identify

• Within hospital management
  – Always necessitates ICU admission?
    • Step down pilot of 20 patients, NIHSS score <15, ICH score <2
    • No transfers to NSICU, no adverse events
• While the science of how to care for patients with ICH and SAH grows rapidly, controversies remain
• Evolving science on management of blood pressure after ICH will likely revise current guidelines
• Continue to watch the science on mobilization, reversal of coagulopathy & management within systems of care closely
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