Tranexamic Acid for Protection in Subarachnoid Hemorrhage (The TAP-SAHTrial)

Christopher Zammit, MD
Opeolu Adeoye, MD MS
E. Sander Connolly, MD
Stephan Mayer, MD
Andrew Ringer, MD
NETT Retreat
10.21.13
Disclosures

• No relevant disclosures
Impact of aSAH

- ~30,000/ year in the US
- Mortality as high as 45%
- Significant morbidity among survivors

Connolly, Stroke 2012
Outcomes following aSAH

- 10% die pre-hospital
- 30% die after admission
- 20% mRS 4-5 at 6 months
- 40% mRS 0-3 at 6 months

Outcomes if Rebleeding

8-23% rebleed after arrival, half of those in first six hours

- 52% die
- 29% mRS 4-5 at 6 months
- 19% mRS 3 at 6 months
- 0% mRS 0-2 at 6 months

Unadjusted Poor Outcomes Attributable to Rebleeding

• 40-60%
Current Data

No proven interventions to prevent rebleeding

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>Antifibrinolytic</th>
<th>Incidence rebleeding, antifibrinolytic vs control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hillman et al. [3]</td>
<td>Randomized, prospective, multicenter study of patients with SAH verified within 48 h of first hospital admission</td>
<td>TXA at diagnosis and every 6 h until aneurysm occlusion or 72 h</td>
<td>2.4 vs. 10.8% ($P &lt; 0.01$)</td>
</tr>
<tr>
<td></td>
<td>$N = 254$ TXA  $N = 251$ controls</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Harrigan et al. [6]</td>
<td>Retrospective review</td>
<td>Short-term EACA administered before aneurysm surgery, which occurred an average of 47 h after admission</td>
<td>1.4%</td>
</tr>
<tr>
<td></td>
<td>$N = 356$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Starke et al. [16]</td>
<td>Prospective, observational study</td>
<td>Short-term EACA before aneurysm treatment</td>
<td>2.7 vs. 11.4% ($P = 0.019$)</td>
</tr>
<tr>
<td></td>
<td>$N = 73$ treated with EACA  $N = 175$ controls</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

• “For patients with an unavoidable delay in obliteration of aneurysm, a significant risk of rebleeding, and no compelling medical contraindications, short term (<72 hours) therapy with tranexamic acid or aminocaproic acid is reasonable to reduce the risk of early aneurysm rebleeding (Class IIa; Level of Evidence B). “
Current US Practice – Clinical Equipoise

- From 2006-2010, only 1.6% of SAH patients received antifibrinolytics
- Midwest and Northeast regions were more likely to give antifibrinolytics

Adeoye, Neurocritical Care Conf 2011
Proposal

- Phase 3 double-blind randomized placebo controlled trial
- Intervention – Tranexamic acid 1gm IV within 12 hours of symptom onset then every six hours for 72 hours or until aneurysm is secured
- Primary Outcome – proportion of good outcome at 6 months using sliding dichotomy for the mRS
- Secondary Outcomes – GOSE at 6 months, Mortality at hospital discharge and 6 months, rebleeding rates, thromboembolic complications
Inclusion Criteria

- CT with acute SAH suspicious for aneurysm rupture
- 18 – 80 years of age
- GCS $\geq$ 6 at time of randomization
- Study drug administered within 3 hours of enrolling hospital arrival
Exclusion Criteria

- Pregnancy
- GCS 3-5
- Fixed dilation of either or both pupils
- Cardiac arrest at any point between ictus and randomization
- Deterioration of $\geq 4$ points on GCS between first medical contact and randomization
- DVT/PE in last 6 months or known hypercoagulable disorder
- STEMI
- NSTEMI
  - Either one of the following:
    - ECG changes c/w ischemia in a vascular distribution with chest pain in conscious patient OR
    - Troponin $> 0.3$ regardless of consciousness or chest pain
Estimated Sample Size – 750 patients in each arm

- Assumptions
  - 60% mRS 0-3 in placebo arm at six months
  - Effect size 7%
  - Binomial distribution, two-sided test, alpha=0.05, beta=0.2
  - Sample size may be reduced with higher proportion of “good outcome” in placebo arm using sliding dichotomy