Cerebral Vasospasm: Current and Emerging Therapies
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Disclosures
• None

Objectives
• Brief Overview
• How we got here
• Review of Trials
• “Meta-analysis”
• Future Directions
Aneurysmal SAH

- ~ 30,000 aneurysmal SAH's each year
- 20 to 40% of these patients will suffer from delayed cerebral ischemia (DCI)
  - Associated with increased morbidity and mortality
  - Cerebral vasospasm is a strong predictor of DCI
- Arterial cerebral vasospasm
  - Evident in up to 70%
  - Symptomatic in 20 to 50%

Delayed Cerebral Ischemia

- Increasing evidence suggests DCI is a multifactorial process
  - Vasospasm only one contributor

How we got here

- Cooperative Study
- Triple-H Therapy
- Nimodipine Trials
- Tirasazad
- CONSCIOUS-2 and CONSCIOUS-3 (Clazosentan)
- MASH-2 (Magnesium sulphate)
- STASH (Simvastatin)
- Future Directions
The Cooperative Study

- Randomized Controlled Trial of patients with aneurysmal subarachnoid hemorrhage
  - 1,005 SAH patients randomized to:
    - Bed Rest
    - Drug-induced hypotension
    - Carotid ligation
    - Intracranial surgery
  - Incidence of Vasospasm: 42%
    - Bed Rest: 42%
    - Drug-induced hypotension: 44%
    - Carotid ligation: 41%
    - Intracranial surgery: 39%

Triple-H Therapy

- Induced hypertension for treatment of “ischemic symptoms” described in 1976 by Kosnik and Hunt
  - Elevated blood pressure improved neurological symptoms in 7 patients
- In 1982, Kassell et. al reported improvement in 58 patients with neurological deterioration and confirmed angiographic vasospasm
  - Improvement in 74%
  - 33% complication rate

Triple-H Therapy

- Awad et. al reported on 118 SAH patients
  - “Symptomatic vasospasm” in 35.6%
  - “Good outcomes” in 34 of 42 patients with vasospasm treated with Triple-H therapy
  - 6.7% Death or Disability
  - 7% complication rate
**Nimodipine** (Only FDA Approved Therapy)  
- In good grade SAH patients (Allen GS, et al. NEJM, 1983)  
  - Diminished neurological deficits (1/56) vs. placebo (8/60) attributed to vasospasm  
- In poor-grade aneurysm (Petruk KC, et al. JNS, 1988)  
  - Better outcome at 3 months (29.2% vs. 9.8%)  
- British aneurysm nimodipine trial (Pickard et al. BMJ 1989)  
  - 554 patients nimodipine vs. placebo  
  - Poor outcome 20% vs. 33% placebo (Risk Reduction of 40%)  
  - 34% angio-negative SAH  
  - 58% did not undergo treatment of an aneurysm

**Tirilazad**  
- An aminosteroid and a potent inhibitor of oxygen radical-induced lipid peroxidation  
- Tirilazad (Europe, Australia, and New Zealand)  
  - Kassell et al. (JNS 1996)  
  - 1,015 patients in RCT of multi-dose tirilazad vs. placebo (+/- nimodipine, +/- prophylactic Triple-H)  
  - 28% poor outcome in high-dose vs. 34% placebo

**Tirilazad (North American Cooperative)**  
- Haley et al. (JNS 1997)  
- 897 patients in RCT of multi-dose tirilazad vs. placebo (+nimodipine, +/- prophylactic Triple-H)  
- No difference in 3 month outcome (placebo 27% poor vs. 30% in treatment arm)
Endothelin Receptor Antagonists

- ET-1 overproduction is a leading theory for pathogenesis of vasospasm

- Clazosentan → endothelin receptor agonist
  - CONSCIOUS-1 (Phase II Trial)
    - clazosentan reduced the frequency of vasospasm in a dose-dependent fashion
    - highest dose was associated with 65% relative risk reduction in vasospasm

CONSCIOUS-II (Phase 3 RCT)

- 1,157 SAH patients undergoing clipping

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Clazosentan</th>
<th>Relative Risk Reduction (95% CI)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or vasospasm-related mortality</td>
<td>21.4%</td>
<td>17.5%</td>
<td>17.4% (17.3%-18.3%)</td>
<td>18.2%</td>
</tr>
</tbody>
</table>

CONSCIOUS-III (Phase 3 RCT)

- 571 SAH patients undergoing coiling
  - Halted prematurely following completion of CONSCIOUS-II
    - Primary Outcome
      - No difference in poor outcome 24% placebo vs. 25% and 28% in treated groups
    - Secondary Outcome:
MASH-2: Magnesium (Phase III RCT)
- Neuroprotective and vasodilatory properties
- Early studies suggested possible benefit in preventing ischemic damage
- Phase 3 RCTs: MASH-2 (1204 patients)
  - IV magnesium did NOT increase the probability of good outcome or decrease risks for cerebral infarction, radiographic vasospasm or mortality
- No evidence to support use

STASH: Simvastatin (Phase III RCT)
- Beneficial effects on endothelial inflammation, oxidative stress, and inhibition of platelet adhesion and aggregation
- 803 SAH patients randomized
- No difference

“Meta-analysis”
- Compare outcomes from Nimodipine Trial to other SAH trials (ISAT and BRAT)

<table>
<thead>
<tr>
<th>Nimodipine Treated Patients</th>
<th>Total Patients</th>
<th>Total Poor Outcome</th>
<th>Proportion w/ Poor Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nimodipine Treated Patients</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>British Nimodipine Trial</td>
<td>278</td>
<td>55</td>
<td>20%</td>
</tr>
<tr>
<td>ISAT - surgical</td>
<td>1063</td>
<td>392</td>
<td>37%</td>
</tr>
<tr>
<td>BRAT - surgical</td>
<td>205</td>
<td>69</td>
<td>34%</td>
</tr>
<tr>
<td>Non-nimodipine Total</td>
<td>1268</td>
<td>461</td>
<td>36%</td>
</tr>
</tbody>
</table>

- 17% reduction in poor outcome in the British Nimodipine Trial compared to ISAT and BRAT
  - 95% CI (11% to 22%) p < 0.0001
- A patient in ISAT or BRAT was 2.3 times more likely to have a poor outcome than a patient treated in the British Nimodipine Trial
  - 95% CI (1.7 to 3.2) p < 0.0001
What gives?

- Peculiar things about Nimodipine and its trials
  - No other Ca2+ channel blocker has been effective
  - We don’t know why it works
    - No effect on angiographic vasospasm
  - Original trials no hypotension
    - Nimodipine discontinued in 1% for hypotension
  - Today up to 30% will have it stopped
  - No study has come close to repeating the effect size seen in the British Nimodipine Trial
    - 34% of patients would be excluded in current trials

Future Directions

A Phase I Clinical Trial
of Sildenafil for the Treatment of Cerebral Vasospasm Following Subarachnoid Hemorrhage

[Day 2, Day 10, Day 23 images]
Sildenafil: A Potential Therapy

- Phosphodiesterase V inhibition
  - In animal models of SAH
    - Reduces larger artery vasospasm
    - Improves neurological outcomes
    - Restores impaired autoregulatory mechanisms
  - In non-SAH humans
    - Augments autoregulatory mechanisms
  - In SAH humans
    - Evidence of improved vasospasm based on TCD

**Nitric Oxide-cGMP pathway**

**Normal Physiology**

- L-arginine
- L-citrulline
- NO
- NO synthase (nNOS)
- cGMP
-PKG
- K+ channel

**SAH**

- Hemoglobin scavenging
- NO
- NO synthase (eNOS)
- cGMP
-PKG
- K+ channel
- Vasospasm
Animal Results

Sildenafil decreases PDE5 activity and cGMP levels after SAH

Animal Results

Sildenafil reduces SAH-induced vasospasm

Animal Results

Sildenafil reduces SAH-induced neuro deficits
Study Design

- A prospective non-randomized Phase I trial investigating sildenafil in a series of controlled dose escalation studies with

Specific Aims:
1. Determine the safety of intravenous sildenafil in SAH patients
2. Assess its ability to reverse angiographic vasospasm
3. Study the effect of intravenous sildenafil on CBF

Methods: Protocol

Two phase protocol
- Phase I - 6 patients
  - Single 10mg low dose
  - Angiography or PET
- Interim safety analysis
- Phase II - 6 patients
  - Two 30mg high doses
  - Angiography AND PET

Protocol: Phase I

- Aneurysmal SAH
  - Screening Angiogram
  - No Vasospasm
    - Exclude
    - Exclude
  - Vasospasm
    - Mild Vasospasm
      - Exclude
      - PET 10mg
    - Moderate/Severe Vasospasm
      - Angiography 10mg
Aneurysmal SAH → Screening Angiogram

- No Vasospasm → Exclude
- ANY Vasospasm
  - Angiography 30mg
  - PET in Following 24 to 48 hours 30mg

**Methods: Angiography and PET**

Following screening angiogram
- Receive sildenafil dose
  - 30 min wait time
- Repeat diagnostic angiogram

PET studies 24 to 48 hours following first sildenafil dose
- Baseline PET: resting CBF
- Receive sildenafil dose
  - 30 min wait time
- Repeat PET: resting CBF

**Analysis: Angiography**

- Blinded reviewers labeled films as
  - Pre-Sildenafil
  - Post-Sildenafil
  - Post-Verapamil (when available)

Reviewers subjectively graded films regarding:
- Location of vasospasm (mild, moderate or severe)
- Improvement vs. No improvement in vasospasm

Un-blinded measurements made between Admission, Pre-Sildenafil, Post-Sildenafil, Post-Verapamil images
- Petrous ICA or proximal vertebral as reference
- Measurements made at highest degree of stenosis in Supraclinoidal ICA, A1, A2, M1 and M2 segments.
Results

- 23 patients enrolled
- 12 patients completed study
  - 6 patients received 10mg dose
    - 5 Angiography
    - 1 PET
  - 6 patients received 30mg dose
- PET unavailable for 4 patients
- 2 patients did not undergo 7-day angio
- 5 patients no vasospasm

Results: Demographics

<table>
<thead>
<tr>
<th>Gender</th>
<th></th>
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<tbody>
<tr>
<td>Male</td>
<td>6 (50%)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>6 (50%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Hunt &amp; Hess Grade</th>
<th></th>
<th></th>
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</thead>
<tbody>
<tr>
<td>II</td>
<td>3 (25%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>4 (33%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>3 (25%)</td>
<td></td>
</tr>
<tr>
<td>V</td>
<td>2 (17%)</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Treatment</th>
<th></th>
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<tbody>
<tr>
<td>Clip</td>
<td>5 (42%)</td>
<td></td>
</tr>
<tr>
<td>Coil</td>
<td>7 (58%)</td>
<td></td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Modified Fisher Grade</th>
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<tbody>
<tr>
<td>I</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>5 (42%)</td>
<td></td>
</tr>
<tr>
<td>IV</td>
<td>6 (50%)</td>
<td></td>
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</table>

<table>
<thead>
<tr>
<th>Aneurysm Location</th>
<th></th>
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<tbody>
<tr>
<td>ACA</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Acomm</td>
<td>5 (42%)</td>
<td></td>
</tr>
<tr>
<td>MCA</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>PICA</td>
<td>1 (8%)</td>
<td></td>
</tr>
<tr>
<td>Pcomm</td>
<td>4 (33%)</td>
<td></td>
</tr>
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</table>

Results: Safety

- No adverse events
- Stable neurological exams following infusion
  - 1 patient with improvement (resolution of pronator drift)
- No adverse effect upon
  - Heart rate
  - Oxygen saturation
  - Intracranial pressure
Results: Blood Pressure

Phase I: 10mg Sildenafil Dose

<table>
<thead>
<tr>
<th>ID</th>
<th>Percent Drop (%)</th>
<th>Return Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>35</td>
<td>40</td>
</tr>
<tr>
<td>2</td>
<td>16</td>
<td>30</td>
</tr>
<tr>
<td>3</td>
<td>13</td>
<td>15</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>16</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>6</td>
<td>0</td>
</tr>
</tbody>
</table>

Average decline in MAP: 16%
Average time to return: 16 mins

Phase II: 30mg Sildenafil Dose, Angiography

<table>
<thead>
<tr>
<th>ID</th>
<th>Percent Drop (%)</th>
<th>Return Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>21</td>
<td>50</td>
</tr>
<tr>
<td>8</td>
<td>34</td>
<td>75</td>
</tr>
<tr>
<td>9</td>
<td>17</td>
<td>20</td>
</tr>
<tr>
<td>10</td>
<td>12</td>
<td>15</td>
</tr>
<tr>
<td>11</td>
<td>15</td>
<td>NR</td>
</tr>
<tr>
<td>12</td>
<td>12</td>
<td>5</td>
</tr>
</tbody>
</table>

Average decline in MAP: 19%
Average time to return: 33 mins

Phase II: 30mg Sildenafil Dose, PET

<table>
<thead>
<tr>
<th>ID</th>
<th>Percent Drop (%)</th>
<th>Return Time (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>18</td>
<td>32</td>
</tr>
<tr>
<td>8</td>
<td>24</td>
<td>55</td>
</tr>
<tr>
<td>9</td>
<td>16</td>
<td>4</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>40</td>
</tr>
<tr>
<td>11</td>
<td>10</td>
<td>0</td>
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</tbody>
</table>

Average decline in MAP: 17%
Average time to return: 27 mins
Results: Angiographic Response

• 7 of 11 (64%) patients with identified improvement (none worsened)

<table>
<thead>
<tr>
<th>ID</th>
<th>Vasospasm Severity</th>
<th>Improve Post-Sildenafil</th>
<th>Maximum Dilatation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Severe</td>
<td>Yes</td>
<td>1.25</td>
</tr>
<tr>
<td>2</td>
<td>Mod</td>
<td>Yes</td>
<td>1.25</td>
</tr>
<tr>
<td>4</td>
<td>Mod</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>5</td>
<td>Mod</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>6</td>
<td>Mod</td>
<td>Yes</td>
<td>0.83</td>
</tr>
</tbody>
</table>

3 of 5 (60%) improved
Average dilatation (all patients): 0.8 mm
Average dilatation (responders): 1.25 mm

30mg Sildenafil Dose

<table>
<thead>
<tr>
<th>ID</th>
<th>Vasospasm Severity</th>
<th>Improve Post-Sildenafil</th>
<th>Maximum Dilatation (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>Mod</td>
<td>Yes</td>
<td>1.25</td>
</tr>
<tr>
<td>8</td>
<td>Severe</td>
<td>Yes</td>
<td>2.1</td>
</tr>
<tr>
<td>9</td>
<td>Mod</td>
<td>No</td>
<td>NA</td>
</tr>
<tr>
<td>10</td>
<td>Severe</td>
<td>Yes</td>
<td>2.1</td>
</tr>
<tr>
<td>11</td>
<td>Severe</td>
<td>Yes</td>
<td>2.25</td>
</tr>
<tr>
<td>12</td>
<td>Severe</td>
<td>Yes</td>
<td>0.6</td>
</tr>
</tbody>
</table>

4 of 6 (67%) improved
Results: Angiographic Response

Pre-sildenafil | Post-sildenafil

Conclusions

Intravenous sildenafil to treat post-SAH cerebral vasospasm is:
- Safe
  - No adverse events
  - Acceptable blood pressure profile
    - Transient 16-19% decline in MAP
- Evidence of a positive angiographic response in select patients (64%)

Future Directions

- Pharmacokinetic/Pharmacodynamic Translational Study
  - Compare pharmacokinetic differences between oral and intravenous sildenafil in SAH patients
  - Determine if oral sildenafil has a more favorable hemodynamic profile
  - Assess the effects of sildenafil on:
    - Cerebral vasospasm measured by transcranial Doppler
    - Cerebral autoregulation
Questions?

Contact Information

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