The management of traumatic subarachnoid hemorrhage and vasospasm with Milrinone

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Disclosures

• None
Outline

• Background information on tSAH and vasospasm
• Introduction to the Milrinone protocol
  – “The Montreal Neurological Hospital Protocol”
• Case presentations (x3)
• Concluding points
Vasospasm and traumatic subarachnoid hemorrhage (tSAH)

- tSAH is the most common lesion encountered after traumatic brain injury (TBI) [1].
- Higher grades of tSAH on the Fisher scale have been shown to predict worse outcomes for TBI patients [2,3,6,7].
- Therefore, vasospasm has been investigated as a possible cause for the inferior outcomes of TBI patients with tSAH.
- The pathophysiology of the vasospasm occurring after aneurysmal SAH and tSAH is extremely similar [4,5].
The Fisher scales

### TABLE 2. Risk of symptomatic vasospasm according to the original and modified Fisher computed tomographic rating scales

<table>
<thead>
<tr>
<th>Modified Fisher scale</th>
<th>Percent classified to grade</th>
<th>Percent within grade with symptomatic vasospasm</th>
<th>Odds ratio&lt;sup&gt;b&lt;/sup&gt;</th>
<th>95% confidence interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Focal or diffuse thin SAH, no IVH&lt;sup&gt;c&lt;/sup&gt;</td>
<td>21.6</td>
<td>24</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>2 Focal or diffuse thin SAH, with IVH</td>
<td>10.8</td>
<td>33</td>
<td>1.58</td>
<td>1.02–2.46</td>
<td>0.042</td>
</tr>
<tr>
<td>3 Thick SAH present, no IVH</td>
<td>33.9</td>
<td>33</td>
<td>1.59</td>
<td>1.14–2.22</td>
<td>0.006</td>
</tr>
<tr>
<td>4 Thick SAH present, with IVH</td>
<td>33.7</td>
<td>40</td>
<td>2.20</td>
<td>1.58–3.05</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Adjusted odds ratio for incremental risk of symptomatic vasospasm for each scale level</td>
<td></td>
<td></td>
<td>1.28</td>
<td>1.06–1.54</td>
<td>0.010</td>
</tr>
</tbody>
</table>

### Fisher scale

| 1 Focal thin SAH                                                                      | 8.1                         | 21                                               | —                      | —                            | —   |
| 2 Diffuse thin SAH                                                                    | 10.9                        | 25                                               | 1.26                   | 0.70–2.23                    | 0.442|
| 3 Thick SAH present                                                                  | 67.7                        | 37                                               | 2.18                   | 1.35–3.51                    | 0.001|
| 4 Focal or diffuse thin SAH, with significant ICH or IVH                             | 13.3                        | 31                                               | 1.71                   | 0.98–2.98                    | 0.060|
| Adjusted odds ratio for incremental risk of symptomatic vasospasm for each scale level |                             |                                                  | 1.1                    | 0.84–1.43                    | 0.488|

<sup>a</sup> SAH, subarachnoid hemorrhage; IVH, intraventricular hemorrhage.

<sup>b</sup> Adjusted values were calculated controlling for other significant predictors of vasospasm (early angiographic vasospasm, history of hypertension, neurological grade, and mean arterial pressure).

<sup>c</sup> Includes 20 patients classified to modified Fisher 0 (no SAH or IVH present).
Vasospasm and traumatic subarachnoid hemorrhage (tSAH)

- Diagnosis is often missed
- Thus far, we use the same treatments as for vasospasm following aSAH:
  1. Triple-H Therapy
  2. Calcium Channel Blockers [9]
- These above therapies have their limitations in trauma patients
- Recently, Milrinone has been used as a vasodilatory agent that can reverse the effects of vasospasm following aSAH
Calcium Channel Blockers

Calcium channel blockers for acute traumatic brain injury (Review)

Langham J, Goldfrad C, Teasdale G, Shaw D, Rowan K
**Analysis 1.6.** Comparison 1 Calcium channel blockers versus control, Outcome 6 Death and severe disability (by participant subgroups).

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 6 Death and severe disability (by participant subgroups)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>n/N Placebo</th>
<th>n/N Peto Odds Ratio</th>
<th>Weight</th>
<th>Peto Odds Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 tSAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT I 1990</td>
<td>26/35</td>
<td>25/36</td>
<td>13.5 %</td>
<td>1.27 [0.45, 3.54]</td>
</tr>
<tr>
<td>HIT II 1994</td>
<td>64/123</td>
<td>87/145</td>
<td>60.7 %</td>
<td>0.72 [0.45, 1.17]</td>
</tr>
<tr>
<td>HIT III 1996</td>
<td>15/60</td>
<td>28/61</td>
<td>25.8 %</td>
<td>0.40 [0.19, 0.85]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>218</td>
<td>242</td>
<td><strong>100.0 %</strong></td>
<td><strong>0.67 [0.46, 0.98]</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>105 (), 140 (Placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 3.35, df = 2 (P = 0.19); I² = 40%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 2.07 (P = 0.038)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 no tSAH</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HIT I 1990</td>
<td>56/141</td>
<td>64/139</td>
<td>36.4 %</td>
<td>0.77 [0.48, 1.24]</td>
</tr>
<tr>
<td>HIT II 1994</td>
<td>96/282</td>
<td>81/269</td>
<td>63.6 %</td>
<td>1.20 [0.84, 1.71]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>423</td>
<td>408</td>
<td><strong>100.0 %</strong></td>
<td><strong>1.02 [0.77, 1.36]</strong></td>
</tr>
<tr>
<td>Total events:</td>
<td>152 (), 145 (Placebo)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 2.09, df = 1 (P = 0.15); I² = 52%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.14 (P = 0.89)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 3.02, df = 1 (P = 0.08), I² = 67%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
**Analysis 1.4. Comparison 1 Calcium channel blockers versus control, Outcome 4 Hypotension.**

Review: Calcium channel blockers for acute traumatic brain injury

Comparison: 1 Calcium channel blockers versus control

Outcome: 4 Hypotension

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Placebo n/N</th>
<th>Peto Odds Ratio</th>
<th>Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Nicardipine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>0/0</td>
<td>0.0 %</td>
<td>0.0 [ 0.0, 0.0 ]</td>
</tr>
<tr>
<td>Total events: 0 (0, 0 (Placebo))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: not applicable</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 Nimodipine

| HIT I 1990 | 3/176 | 0/175 | 2.7 % | 7.43 [ 0.77, 71.91 ] |
| HIT II 1994 | 71/423 | 47/429 | 91.4 % | 1.63 [ 1.10, 2.40 ] |
| HIT III 1996 | 5/60 | 2/61 | 60.0 % | 2.51 [ 0.55, 11.47 ] |

| **Subtotal (95% CI)** | 659 | 665 | 100.0 % | 1.74 [ 1.20, 2.52 ] |
| Total events: 79 (49, 49 (Placebo)) |
| Heterogeneity: Chi^2 = 1.90, df = 2 (P = 0.39); I^2 = 0.0% |
| Test for overall effect: Z = 2.93 (P = 0.0034) |

| **Total (95% CI)** | 659 | 665 | 100.0 % | 1.74 [ 1.20, 2.52 ] |
| Total events: 79 (49, 49 (Placebo)) |
| Heterogeneity: Chi^2 = 1.90, df = 2 (P = 0.39); I^2 = 0.0% |
| Test for overall effect: Z = 2.93 (P = 0.0034) |
| Test for subgroup differences: Not applicable |
The Montreal Neurological Hospital Protocol

Milrinone and Homeostasis to Treat Cerebral Vasospasm Associated with Subarachnoid Hemorrhage: The Montreal Neurological Hospital Protocol

Marcelo Lannes · Jeanne Teitelbaum · Marla del Pilar Cortés · Mauro Cardoso · Mark Angle
Fig. 1 Flowchart illustrating the Montreal Neurological Hospital protocol. *HCP* hydrocephalus, *CVP* central venous pressure, *BP* blood pressure, *MAP* mean arterial pressure.
Case #1

• 78 year-old male, right-handed
• PMHx: A. Fib (on Coumadin), HTN, DM2, CAD
• Presented to the ER after falling down four steps
• **GCS = 15 on arrival**, no focal neurological deficits
Case #1

Fisher Grade 3 tSAH
Case #1

• On the sixth day, found to be somonolent (GCS 13), dysarthric, apathic and to have a right hemiparesis
• Ct-Head repeated: No acute changes
• Milrinone protocol is started
• His neurological defects are rapidly reversed in the ICU
• Over the following six days, a slow wean off the protocol is necessary as a recurrence of his symptoms was encountered
Case #1

- A Ct-Angiogram was not completed as the patients’ creatinine values were elevated (ARF)
- Transcranial doppler images were inconclusive as there was no available temporal bone window
- He was discharged without any neurological deficits
- GOS = 5 There was no evidence of any ischemic lesion on the follow-up Ct scan done after discharge
Case #2

- 65 year-old female, *right-handed*
- PMHx: *Alcoholism*
- Presented to the ER after falling from her own height *while intoxicated!*
- GCS = 14 *(disoriented)* on arrival, no focal neurological deficits
Case #2 – Ct C-

Fisher Grade 3 tSAH
Case #2

- On the seventh day, she is found to be somonolent (GCS 13), dysarthric, apathic and to have a right hemiparesis
- Ct-Head repeated: No acute changes
- Milrinone protocol is started
- Her neurological deficits are rapidly reversed in the ICU
- Over the following 8 days, a slow wean off the protocol is necessary as a recurrence of symptoms was encountered
Case #2

- A Ct-Angiogram was not completed as the her creatinine value was elevated (ARF)
- A Transcranial dopplers was inconclusive as there was no available temporal bone window
- She was discharged without any neurological deficits
- GOS = 5
- There was no evidence of any ischemic lesion on the follow-up Ct scans done after discharge
Case #3

- 64 year-old male, right-handed
- PMHx: Cerebral abscess, epilepsy
- Presented to the ER after a generalized tonic-clonic seizure and a fall from own height
- GCS = 14 on arrival, no focal neurologic deficit
- Discharged home 3 days post-trauma

Fisher Grade 3 tSAH
Case #3

• 8 days post-trauma, his wife finds him to be **aphasic** with a **right hemiparesis**

• MRI-Brain reveals *ischemic changes in the left middle cerebral artery territory*

• Vasospasm is suspected...
Case #3

- Angiogram confirms vasospasm
- Patient is transferred to the ICU and started on the Milrinone protocol
- Hemiparesis and aphasia improve but not back to the patient’s baseline functioning
- GOS = 4

Segments M1 and M2 of the left middle cerebral artery are vasospastic
Conclusion

• tSAH is the most common traumatic lesion after TBI
• Vasospasm can potentially complicate these cases and cause devastating neurological sequelae
• This complication can be easily missed by the treating team
• Literature is very limited as to recommending the best treatment options for this pathology
• Our 3 cases suggest, for the first time, that Milrinone has the potentiel to treat, without significant complications, cerebral vasospasm after tSAH
• Prospective studies are necessary to develop protocols to help in detecting vasospasm after TBIs and to establish the best treatments
References

2. Eisenberg , H et al. Initial CT findings in 753 patients with severe head injury: A report from the NIH Traumatic Coma Data Bank. JNS. 1990