Delayed cerebral ischemia post subarachnoid hemorrhage

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Proposed definition of clinical deterioration due to delayed cerebral ischemia
Confirmatory testing is often necessary particularly in comatose patients

A = Cerebral blood flow
B = Cerebral blood volume
C = Mean transit time (MTT)
This talk presents a milrinone-based approach to treat delayed cerebral ischemia (DCI) following SAH.
The release of mediators from the degradation of blood seems to be the triggering factor
Inflammation and Cerebral Vasospasm After Subarachnoid Hemorrhage

Gustavo Pradilla

Neurosurgery Clinics of North America 2010

LEGEND

- Extracorpulsular hemoglobin
- Haptoglobin
- CD163 receptor
- sialyl-LewisX
- LFA-1
- Mac-1
- E-selectin
- ICAM-1

ROLLING ADHESION

C1

Neutrophil/Macrophage

C2

Endothelial cell

C3

RBC's

C4

sialyl-LewisX

Nitric Oxide (NO)

Aneurysm rupture

A

Extracorpulsular hemoglobin

Inflammation and Cerebral Vasospasm After Subarachnoid Hemorrhage

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VASOSPASM

Endothelins

APOPTOSIS

Free radicals

Cytokines
Subarachnoid hemorrhage

Transient global ischemia

Subarachnoid blood

Cortical spreading ischemia

Vasospasm

Inflammation/oxidative stress

Microthrombi

Focal cerebral infarctions

Global cerebral atrophy

Poor outcome

R. Loch Macdonald in Cerebral Vasospasm, 2013 Springer Verlag
Pathophysiology involves much more complex than simple vasoconstriction

Angiographic vasospasm is much more frequent than symptomatic vasospasm
Mortality

<table>
<thead>
<tr>
<th>No vasospasm</th>
<th>Vasospasm</th>
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<tbody>
<tr>
<td>18%</td>
<td>42%</td>
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There seems to have a trend towards better outcomes in the 1990’s

Mortality and Morbidity

- Mortality
- Severe disability

Mortality and Morbidity

<table>
<thead>
<tr>
<th>%</th>
<th>Mortality</th>
<th>Severe disability</th>
</tr>
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<tbody>
<tr>
<td>20</td>
<td></td>
<td>23</td>
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chart showing a comparison of mortality and severe disability percentages.
1960’s: Reversal of focal deficits with pressors (Wise et al)

1972: Improvement in vasospasm symptoms with higher BPs

1976: Flamm et al: aminophyilline and isoproterenol
Kassell: 58 patients with vasospasm

Allen: clinical trial nimodipine

Pickard: Largest trial nimodipine

1982

1983

1989

1990’s

Triple H era
Hypervolemia

Triple H became the standard therapy without solid evidence from proper clinical trials.
Incidence of ischemia

Triple H became the standard therapy without solid evidence from proper clinical trials.
Triple H became the standard therapy without solid evidence from proper clinical trials

Complications
There is increasing evidence against the use of hemodilution

**Effects of isovolemic hemodilution**

<table>
<thead>
<tr>
<th></th>
<th>Before hemodilution</th>
<th>After hemodilution</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global Cerebral Blood Flow</td>
<td>7.94</td>
<td>58.56</td>
</tr>
<tr>
<td>Global Cerebral O₂ Delivery</td>
<td>52.25</td>
<td>6.98</td>
</tr>
</tbody>
</table>

There is increasing evidence against the use of hemodilution.

Effects of hypervolemic hemodilution

- Global Cerebral Blood Flow
- Global Cerebral O2 Delivery

Hypertension seems to increase CBF, but effects are inconsistent
Figure 3  Internal carotid artery (ICA) inlet pressure versus percentage reduction in middle cerebral artery (MCA) diameter. Hct, hematocrit.

Joe Sam Robinson, M. Sami Walid, Sinjae Hyun, Robert O'Connell, Chris Menard, Brandi Bohleber

Computational Modeling of HHH Therapy and Impact of Blood Pressure and Hematocrit

Only Class I (beneficial) level A (RCTs) therapy is nimodipine

Statins: conflicting evidence

Magnesium: no impact on outcome

Other calcium channel blockers: no effect
Only Class I (beneficial) level A (RCTs) therapy is nimodipine

Clazosentan: no effect (2 phase III trials)

Tirilazad: no effect

Cisternal thrombolysis: maybe

Prophylactic angiospasty:
Standard therapy is what is recommended by panels and consensus meetings.

Neurocritical care society’s consensus conference 2011

Recommendations:
Now it is called Augmentation Therapy
Standard therapy is what is recommended by panels and consensus meetings

Euvolemia

Titrated hypertensive therapy

Cardiac output augmentation (maybe)

Endovascular therapy as rescue
Identification of multiple PDEs in brain tissue

Animal studies: Aminophylline, papaverine, ascorbic acid

Khajavi: Milrinone in animal model of vasospasm

PDE type IV predominates in cerebral vessels
2001

Arakawa: 1st use in humans with vasospasm; 7 patients

2008

Fraticelli: Prospective series 22 patients

2009

Romero: Intra-arterial milrinone as rescue therapy

2012

Lannes: Case series 88 patients; milrinone-based protocol

?
Milrinone acts at different pathways thought to be involved in the pathophysiology of vasospasm

- Vasodilation
- Reduced platelet aggregation
- Reduced markers of inflammation
- Reduced release of neutrophil elastase
- Reduced apoptotic signaling
Other PDE inhibitors are also being investigated

Cilostazol

Sildenafil
The study by Fraticelli (2008) used milrinone as a complement to hypertension and hypervolemia.
<table>
<thead>
<tr>
<th>WFNS score I</th>
<th>12/22 patients (55%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of norepinephrine</td>
<td>4 patients</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (9%)</td>
</tr>
<tr>
<td>Minimal disability</td>
<td>18 patients (82%)</td>
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2 patients lost to follow-up
The MNH protocol uses milrinone as the primary therapy for DCI
The MNH protocol uses milrinone as the primary therapy for DCI
Retrospective series including all the patients treated for delayed cerebral ischemia

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<tr>
<th>Category</th>
<th>Count/Percentage</th>
</tr>
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<tbody>
<tr>
<td>Hunt and Hess grade I-III</td>
<td>66 (75%)</td>
</tr>
<tr>
<td>Use of norepinephrine</td>
<td>60 (68%)</td>
</tr>
<tr>
<td>Mean duration of therapy</td>
<td>9.8 days</td>
</tr>
<tr>
<td>Deaths</td>
<td>5 (5.7%)</td>
</tr>
<tr>
<td>Good outcome</td>
<td>66 (75%)</td>
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The way we do it at the MNH:

- Triggers: No other causes
- Milrinone: 0.1-0.2mg/kg
- 0.75 mcg/kg/min
- MAP at baseline
The way we do it at the MNH:

- No change after 30 min
- Increase Q 30 min up to 2.5 mcg/kg/min
- If 1.25 mcg/kg/min & no change
- Norepi MAP ≥ 100
  Repeat bolus
The way we do it at the MNH:

1. Emergency angiogram
2. IA milrinone
3. ± Angioplasty
4. No change after 30 min
In conclusion:

We have for over three decades used a standard therapy with significant side effects despite very little evidence to support it.

We should avoid repeating the same mistake.