Brain cooling in acute stroke

SSNF Perth 2015
Developing new treatments for old diseases

Understand
- Understand what causes the disease
- Understand which biological processes are pivotal and which are not

Influence in models
- Be able to change these processes in experiments
- Be able to change outcome in disease models
- Know your treatment is probably safe

Prevent in real life
- Show, in clinical trials, that the treatment changes outcome
- Show that the treatment works in the real world
1026 interventions in experimental stroke

- In vitro and in vivo: 1026
- Tested in vivo: 603
- Effective in vivo: 374
- Tested in clinical trial: 97
- Effective in clinical trial: 1

O’Collins et al, 2006
High blood pressure in animal stroke studies – NXY-059

Hypertension:
- 7% of animal studies
- 77% of patients in the (neutral) SAINT II study

![Graph showing the reduction in infarct volume between hypertensive and normotensive groups with a p-value of <0.001.](image)
High blood pressure in animal stroke studies – tPA

**Infarct Volume:**
- 113 publications
- 212 experiments
- 3301 animals
- Improved outcome by 24% (20-28)

**Hypertension:**
- 9% of animal studies
- Specifically exclusion criterion in (positive) NINDS study
Time to treatment in animal stroke studies

- Both tPA and tirilazad appear to work in animals
- tPA works in humans but tirilazad doesn’t
- Time to treatment: tPA:
  - Animals – median 90 minutes
  - Clinical trial – median 90 minutes
- Time to treatment: tirilazad
  - Animals – median 10 minutes
  - Clinical trial - >3 hrs for >75% of patients
Cooling for stroke

• Cooling seems to work in patients who have brain injury due to cardiac arrest
• There’s lots of stories about individual patients who should have extensive brain damage but don’t
• Many labs use cooling as a positive control in their animal studies
• Preliminary evidence from clinical trials in stroke is encouraging
How to become cool
Evidence based trial design

Experimental Studies

Clinical Trial

Systematic review and meta-analysis
- how powerful is the treatment?
- what is the quality of evidence?
- what is the range of evidence?
- is there evidence of a publication bias?
- What are the conditions of maximum efficacy?
How powerful is the treatment in animals?

101 publications
222 experiments
3256 animals

43.5% protection (40.1-47.0)
What is the quality of evidence?

Reduction in Infarct Volume

favours hypothermia  favours control

Randomised
Non-randomised

Unblinded Assessment
Blinded Assessment

Summary
What is the quality of evidence?
What is the range of evidence?

Sex

Summary

- Mixed
- Female
- Male
- Unknown

Reduction in Infarct Volume
What is the range of evidence?

duration of ischaemia

Summary

- Permanent
- Temporary
- Thrombotic

favours hypothermia  favours control

Reduction in Infarct Volume

-100  50  0  -50
What is the range of evidence?

presence of hypertension
<table>
<thead>
<tr>
<th>Intervention</th>
<th>Reported Effect Size (95% CI)</th>
<th>Bias with Egger Regression</th>
<th>Bias with METATRIM</th>
<th>Additional % Studies Considered “Missing”</th>
<th>METATRIM Adjusted Effect Size (95% CI)</th>
<th>Absolute Overstatement of Efficacy</th>
<th>Relative Overstatement of Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estrogens</td>
<td>26.7% (20.4%–33.0%)</td>
<td>+</td>
<td>+</td>
<td>24</td>
<td>11.9% (4.6%–19.2%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>14.8% (8.0%–21.6%)</td>
<td>124.4%</td>
</tr>
<tr>
<td>FK506</td>
<td>32.0% (27.8%–36.3%)</td>
<td>+</td>
<td>+</td>
<td>30</td>
<td>21.9% (17.5%–26.3%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>10.1% (5.8%–14.4%)</td>
<td>46.1%</td>
</tr>
<tr>
<td>Growth factors</td>
<td>29.7% (25.9%–33.4%)</td>
<td>+</td>
<td>+</td>
<td>14</td>
<td>25.1% (21.2%–28.9%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>4.6% (0.9%–8.3%)</td>
<td>18.3%</td>
</tr>
<tr>
<td>Hypothermia</td>
<td>43.5% (40.1%–47.0%)</td>
<td>+</td>
<td>+</td>
<td>20</td>
<td>35.4% (31.7%–39.1%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>8.1% (4.5%–11.6%)</td>
<td>22.9%</td>
</tr>
<tr>
<td>IL1-RA</td>
<td>38.2% (31.2%–45.1%)</td>
<td>+</td>
<td>+</td>
<td>36</td>
<td>25.4% (18.4%–32.4%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>12.8% (5.9%–19.7%)</td>
<td>50.4%</td>
</tr>
<tr>
<td>Melatonin</td>
<td>42.1% (35.7%–48.5%)</td>
<td>+</td>
<td>+</td>
<td>14</td>
<td>41.0% (34.8%–47.3%)</td>
<td>1.1% (−5.1% to 7.4%)</td>
<td>2.7%</td>
</tr>
<tr>
<td>Minocycline</td>
<td>30.9% (24.1%–37.6%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Nicotinamide</td>
<td>29.2% (23.0%–35.5%)</td>
<td>+</td>
<td>+</td>
<td>24</td>
<td>21.8% (14.9%–28.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.4% (0.8%–13.9%)</td>
<td>33.9%</td>
</tr>
<tr>
<td>NOS donors</td>
<td>21.4% (13.7%–29.1%)</td>
<td>+</td>
<td>+</td>
<td>25</td>
<td>14.0% (6.4%–21.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.4% (−0.1% to 14.9%)</td>
<td>52.9%</td>
</tr>
<tr>
<td>NOS inhibitors</td>
<td>22.2% (17.1%–27.3%)</td>
<td>+</td>
<td>+</td>
<td>13</td>
<td>14.7% (8.9%–20.6%)&lt;sup&gt;a&lt;/sup&gt;</td>
<td>7.5% (2.0%–13.0%)</td>
<td>51.0%</td>
</tr>
<tr>
<td>NXY-059</td>
<td>43.8% (34.7%–52.8%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Piracetam and related compounds</td>
<td>29.6% (16.1%–44.4%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Stem cells</td>
<td>29.6% (23.7%–35.4%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>Tirilazad</td>
<td>31.9% (23.1%–40.7%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td>tPA</td>
<td>22.5% (19.2%–25.9%)</td>
<td>+</td>
<td>+</td>
<td>5</td>
<td>19.9% (16.4%–23.3%)</td>
<td>2.6% (−0.7% to 6.0%)</td>
<td>13.1%</td>
</tr>
<tr>
<td>Other Thrombolytics</td>
<td>46.6% (35.7%–57.5%)</td>
<td>+</td>
<td>−</td>
<td>0</td>
<td>No adjustment</td>
<td>No adjustment</td>
<td>No adjustment</td>
</tr>
<tr>
<td><strong>Pooled analysis</strong></td>
<td><strong>31.3% (29.7%–32.8%)</strong></td>
<td>+</td>
<td>+</td>
<td><strong>214</strong>&lt;sup&gt;b&lt;/sup&gt;</td>
<td><strong>23.8% (22.2%–25.5%)</strong>&lt;sup&gt;a&lt;/sup&gt;</td>
<td><strong>7.5% (5.9%–9.1%)</strong></td>
<td><strong>31.1%</strong></td>
</tr>
</tbody>
</table>
What are the conditions of maximum efficacy?

duration of hypothermia

Summary

- 0 to 105 mins
- 110 to 130 mins
- 135 to 180 mins
- 195 to 480 mins
- 960 to 4470 mins

favours hypothermia  favours control

Reduction in Infarct Volume
What are the conditions of maximum efficacy?

delay to treatment

Pretreatment
- 0 - 29 min
- 30 - 59 min
- 60 - 89 min
- 90 - 179 min
- 180 - 359 min
- 360 min

Summary
What are the conditions of maximum efficacy?

**depth of hypothermia**

- 24 to 29°C
- 30°C
- 31°C
- 32°C
- 33°C
- 34°C
- 35°C

**Summary**

Reduction in Infarct Volume
# EuroHYP-1

## Knowledge translation table

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Animal data</th>
<th>EuroHYP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>How powerful is the treatment?</td>
<td>&gt;40% improvement in outcome</td>
<td>Powered to detect 7% improvement in outcome</td>
</tr>
<tr>
<td>What is the quality of evidence?</td>
<td>Efficacy maintained in high quality studies</td>
<td>Randomised, blinded outcome assessment, intensely monitored</td>
</tr>
<tr>
<td>Is there evidence of a publication bias?</td>
<td>Yes, but &gt;35% improvement in adjusted outcome</td>
<td>Registered</td>
</tr>
<tr>
<td>What is the range of evidence?</td>
<td>Good: sex, duration, delay to treatment, intensity, hypertension, reperfusion</td>
<td>Patients &gt;18yo with acute ischaemic stroke, NIHSS 6 to 20, treated within 6hrs</td>
</tr>
<tr>
<td>What are the conditions of maximum efficacy?</td>
<td>Temperature dependent: otherwise robust across dimensions</td>
<td>Target 34-35°C</td>
</tr>
</tbody>
</table>
EuroHYP-1

• International randomised controlled clinical trial of modest cooling in patients with stroke
• Evidence based trial design
  – entry within 6 hours of stroke onset
  – Cooling to 34 to 35°C
  – Patients with hypertension allowed
  – Cooling for 24 hours
EuroHYP-1

- FP7 funding of €11m awarded from 01/02/12
- Target 50 – 70 centres in more than 15 countries
- First patient recruited November 2013
- 1500 patient target over 4 years
- Results late 2017
# Performance by country

<table>
<thead>
<tr>
<th></th>
<th>Germany</th>
<th>UK</th>
<th>Denmark</th>
<th>France</th>
<th>Spain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre months open</td>
<td>277.77</td>
<td>70.33</td>
<td>16.10</td>
<td>7.63</td>
<td>8.60</td>
</tr>
<tr>
<td>Patients Randomised</td>
<td>20</td>
<td>14</td>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Patients per centre Month</td>
<td>0.072</td>
<td>0.199</td>
<td>0.186</td>
<td>0.131</td>
<td>0.349</td>
</tr>
</tbody>
</table>
Protocol amendments

• Reduced duration of cooling
• Reduced target sample size
  – Improved ascertainment of mRS
  – mRS shift analysis
  – Covariate adjustment
Thank you

• If you are interested in joining the trial, contact Bridget.Colam@ed.ac.uk