Myth or Reality?
There are limited treatments in ischemic stroke.

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OUTLINE

- Neuroprotection
- Acute medical reperfusion
- Acute interventional reperfusion
- Management of malignant oedema
- Stroke unit management
- Stroke recovery
Neuroprotection

- Prevent/limit cell death in ischemia
- Target the ischemic penumbra
  - Tissue under ischemia, not dead
- Through the ischemic cascade
Neuroprotection

- Many potential agents from bench work
- None have been shown to be beneficial in clinical trials
  - No clinical benefit
  - Methodological and power issues
- Being studied with promise: Citicholine
There is limited treatment with neuroprotection in ischemic stroke
Myth or Reality?

REALITY
Acute medical reperfusion
NINDS: Benefits of IV alteplase

- IV alteplase within 3 hours of stroke onset
- 0.9 mg/kg
  - 10% as bolus then 90% as infusion over 1 hour

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TISSUE PLASMINOGEN ACTIVATOR FOR ACUTE ISCHEMIC STROKE

THE NATIONAL INSTITUTE OF NEUROLOGICAL DISORDERS AND STROKE rt-PA STROKE STUDY GROUP*

Volume 333  DECEMBER 14, 1995  Number 24

NEJM 1995
Functional Outcome

- **Modified Rankin score**

0  No symptoms
1  Symptoms, Able to carry out all usual activities
2  Slight disability, Able to look after own affairs
3  Moderate, Able to walk without assistance
4  Moderately severe, Unable to walk attend to bodily needs without assistance
5  Severe, bedridden, incontinent requiring constant nursing care
6  Dead
NINDS: Benefits of IV alteplase

- mRS 0-1 at 3 months
  - 39% tPA vs 26% placebo
  - OR 1.7; 30% RRR; 13% ARR; NNT 8

- Improvement of mRS by 1 point
  - NNT 3

NEJM 1995
Saver, Arch Neurol 2004
NINDS: Risks of IV alteplase

- sICH = haemorrhage on 24 h CT + clinical suspicion of haemorrhage or decline in neurological status

  - sICH Alteplase 6.6%, Placebo 0.6%

  - Number needed to harm: mRS 4-6 due to sICH = 126

- MORTALITY: no significant difference

  - Alteplase 17% vs Placebo 21%; P=0.30

  NEJM 1995
  Saver, Stroke 2007
ECASS III: RCT 3 to 4.5 hours

Thrombolysis with Alteplase 3 to 4.5 Hours after Acute Ischemic Stroke

- At 3 months, mRS 0-1
- tPA 52.4%, Placebo 45.2%
- ARR 7.2%, NNT 14
- Adjusted OR 1.41 (1.02- 1.98)

Hacke, NEJM, 2008
## ECASS III: Risks

<table>
<thead>
<tr>
<th></th>
<th>tPA</th>
<th>Placebo</th>
<th>P value</th>
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<tbody>
<tr>
<td>Death</td>
<td>7.7%</td>
<td>8.4%</td>
<td>0.68</td>
</tr>
<tr>
<td>sICH (NINDS)</td>
<td>7.9%</td>
<td>3.5%</td>
<td>0.006</td>
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*NINDs = haemorrhage on 24 h CT + clinical suspicion of haemorrhage or decline in neurological status*
Treat as early as possible

- At 3 months, OR for good outcome
  - 0-90 2.2 (1.8 to 4.5)
  - 91-180 1.6 (1.1 to 2.2)
  - 181-270 1.4 (1.1 to 1.9)
  - 271-360 1.2 (0.9 to 1.5)

[Graph showing adjusted odds ratio vs. OTT (min)]

Hacke, Lancet 2004
Selection strategies beyond 4.5

Selecting patients with greater potential to benefit

- ISCHAEMIC PENUMBRA
- ARTERIAL OBSTRUCTION

Excluding patients with higher sICH risk

- LARGE DWI LESION
- EXTENSIVE LEUKOARAIOSIS
Desmoteplase  Tenecteplase

Compared to alteplase,

- Greater fibrin specificity
- Shorter $T \frac{1}{2}$
Summary

- IV alteplase within 4.5 hours improves functional outcome
- Strategies to widen time window being studied
- New agents with promising evidence
There is limited treatment with acute medical reperfusion in ischemic stroke

Myth or Reality?

MYTH
Acute interventional reperfusion
Intra-arterial thrombolysis

Drug aids survival from stroke

By dripping clot-busting drug tPA directly onto a clot through a catheter, it does not have to make its way through the bloodstream.

Catheter feeds the clot-busting drug tPA

Clot

Vein

Catheter is fed from the femoral artery in the groin to the clot in the brain.

SOURCE: American Heart Association
PROACT II

- 0-6 hours
- M1 or M2 occlusion TIMI 0-1
- IA urokinase + heparin VS heparin alone

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<tr>
<th>r-proUK Group</th>
<th>Control</th>
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<tbody>
<tr>
<td>No.</td>
<td>mRS ≤2 No. (%)</td>
</tr>
<tr>
<td>121</td>
<td>(40)†</td>
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No FDA approval
Treatment option in ASA guidelines
Prourokinase no longer available

Furlan, JAMA 1999
Other interventional reperfusion strategies

- Thrombectomy
- Angioplasty and Stenting
- Combination therapy
Summary

- **Intra-arterial thrombolysis**
  - Proven

- **Other strategies**
  - In principle, recanalisation is achieved
  - Clinical outcome studies pending
There is limited treatment with acute interventional reperfusion in ischemic stroke
Myth or Reality?

MYTH
Management of malignant oedema

- Up to 10% of supratentorial infarcts
- Occurs at day 2-5
- Poor outcome
  - 80% mortality
  - Severely disabled
Decompressive Hemicraniectomy

- DECIMAL, DESTINY and HAMLET
  - Slow recruitment $\rightarrow$ planned pooling

- Inclusion
  - 18-60 years
  - Space-occupying MCA
    - NIHSS $>$ 15
    - $>$ 50% MCA of $>$ 145 mL lesion
    - Some impairment of conscious level
  - Within 48 hours

Vahedi, Lancet Neurol 2007
Decompressive Hemicraniectomy

- **Procedure**
  - Large bone flap
    - At least 12 cm diameter
    - Involving frontal, temporal and parietal bones
  - Duraplasty with patch

Vahedi, Lancet Neurol 2007
10 patients treated, 5 more survive
- 1 mild disability
- 1 moderate disability
- 3 moderate-to-severe disability (unable to walk indep)

Vahedi, Lancet Neurol 2007
Subgroups

- Surgery was beneficial ($p<0.01$) in all predefined subgroups with no effect interactions
  - age [above and below 50 years]
  - presence of aphasia
  - time to randomisation [above and below 24 h]
After 48 hours

- HAMLET data alone up to 96 hours
  - No difference in functional outcome
  - Reduced mortality
Summary

- Decompressive hemicraniectomy within 48 hours in patients with malignant MCA syndrome
  - Reduced mortality
  - Improved functional outcome (though there will likely to some disability)
There is limited treatment with neuroprotection in ischemic stroke Myth or Reality?

MYTH
Stroke unit management

- **What is a stroke unit?**
  - geographically defined area
  - multidisciplinary team with training in stroke care
Stroke Unit Management

- **Benefits**
  - reduces mortality: At 1 yr OR 0.79, NNT 26
  - improves functional outcomes: At 1 yr death & dependency OR 0.82
  - advantages extending to 10 years after stroke
  - benefits replicated outside trial setting
  - cost-effective manner
  - applicable to all patients

- **Risks:** None
How does stroke unit management improve outcome?

**COMBINATION OF FACTORS including:**

- screening for dysphagia
- prophylaxis of deep vein thrombosis and other complications
- lipid profile during hospital stay
- diagnosis of pathological mechanism and tailored secondary prevention
- encouragement to stop smoking
- stroke education for patients and family
- early coordinated planning of rehabilitation/discharge (physical, occupational, speech)
- start of antithrombotic medications within 48 h
- prescription of antithrombotic medication at discharge
- prescription of anticoagulants at discharge
- access to vascular and neurosurgeons
There is limited treatment with stroke unit management in ischemic stroke
Myth or Reality?

MYTH
Stroke recovery

- Non-pharmacological management
  - Including therapy

- What about medical treatment?
  - SSRI fluoxetine
  - Neuroaid
SSRI Fluoxetine

- Basic science: neuroprotection and promotion of hippocampal neurogenesis
- Overactivation of motor cortex on functional MRI and transcranial magnetic stimulation
- 4 few small clinical trials: suggest positive effect
Fluoxetine for motor recovery after acute ischaemic stroke (FLAME): a randomised placebo-controlled trial

- Randomised, blinded, n=118
- Fluoxetine 20 mg OM versus Placebo
- Physiotherapy as per normal protocol
- Similar baseline characteristics

**INCLUSION**
- Acute ischemic stroke within 5-10 days
- Hemiparesis/ hemiplegia
- Fugl-Meyer motor scale <55 (100 is normal)

**EXCLUSION**
- NIHSS>20
- Previous disability
- Aphasia
- Problems with comprehension
- Depression
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<th>Fluoxetine</th>
<th>Placebo</th>
<th>P value</th>
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<tr>
<td>Mean FMSS change</td>
<td>34.0</td>
<td>24.3</td>
<td>0.003</td>
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<tr>
<td>Median day 90 FMSS</td>
<td>59</td>
<td>29</td>
<td>0.0006</td>
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<tr>
<td>Mean day 90 NIHSS motor</td>
<td>4.7</td>
<td>6.3</td>
<td>0.012</td>
</tr>
<tr>
<td>Day 90 mRS 0-2 (Functional independence)</td>
<td>26%</td>
<td>9%</td>
<td>0.015</td>
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FLAME conclusions

- Improvement in motor scores
  - Both the FMSS and NIHSS
- Higher likelihood of functional independence

- Side effects: 25% vs 11% with GI side effects
NEUROAID

- Neuroaid- 14 TCM herbs
- Case reports
- 2 RCTs in comparison to other TCM
  - Improves recovery
- Pilot data of 40 subjects
  - Trends demonstrated
- Basic science
  - Reduced necrosis and apoptosis in 4 vessel occlusion mice model
  - Improves functional recovery
CHIMES study

- RCT of 1100 subjects (at 950 now)
- Primary outcome of functional outcome (mRS)
- Safety data: no lab differences, well-tolerated
There is limited treatment with stroke recovery in ischemic stroke
Myth or Reality?

HEADING TO REALITY BUT NOT QUITE THERE YET

FLAME: small, promising treatment option with SSRI
CHIMES: new potential agent

NOT routine in clinical practice currently
There is limited treatment in ischemic stroke in terms of:

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<tr>
<td>Stroke recovery</td>
<td>Nearly MYTH</td>
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Thank you