Stroke Thrombolysis

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May 2014
• Introduction

• Stroke thrombolysis (evidence, complication)

• Clot retrieval

• Stroke thrombolysis (North Wales)
Global burden of stroke

• Third leading cause of death (ischaemic heart disease, cancer)
• Leading cause of disability in adults
• Second leading cause of dementia (Alzheimer’s disease)
Global burden

- At any one time 30-40 beds are occupied
- 6% of total health and social resources
- 11% of deaths
Incidence of stroke

- 174-216 per 100,000 per year
- Prevalence 600-800 per 100,000
- Recurrent stroke is 30-43% in 5 years
Stroke Thrombolysis
THREE STROKE TYPES

Focal Brain Dysfunction

Ischemic Stroke
- Clot occluding artery
  - 85%

Intracerebral Hemorrhage
- Bleeding into brain
  - 10%

Subarachnoid Hemorrhage
- Bleeding around brain
  - 5%

Diffuse Brain Dysfunction
Pharmacology

- Alteplase is an enzyme
- Binds to fibrin in clots
- Converts plasminogen to plasmin
- Plasmin initiates local fibrinolysis
- Circulating fibrinogen drops by a third
- Half life distribution 5 min
  excretion 40 min
# Thrombolysis for AMI

## Table: Cumulative Randomized Controlled Trials (RCTs)

<table>
<thead>
<tr>
<th>Year</th>
<th>RCTs</th>
<th>Pts</th>
</tr>
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<tbody>
<tr>
<td>1960</td>
<td>1</td>
<td>23</td>
</tr>
<tr>
<td>1965</td>
<td>2</td>
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<td>1970</td>
<td>4</td>
<td>316</td>
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<td>1975</td>
<td>10</td>
<td>2544</td>
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<td>1980</td>
<td>23</td>
<td>5757</td>
</tr>
<tr>
<td>1985</td>
<td>30</td>
<td>8340</td>
</tr>
<tr>
<td>1990</td>
<td>70</td>
<td>48154</td>
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</table>

## Diagram: Odds Ratio (Log Scale)

- **P < .01**
- **P < .001**
- **P < .00001**

## Textbook/Review Recommendations

<table>
<thead>
<tr>
<th>Routine</th>
<th>Specific</th>
<th>Rare/Never</th>
<th>Experimental</th>
<th>Not Mentioned</th>
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<tbody>
<tr>
<td>21</td>
<td>5</td>
<td>10</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>1</td>
<td>2</td>
<td>8</td>
<td>7</td>
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<td>2</td>
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</tr>
<tr>
<td>6</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

- Favors Treatment
- Favors Control
National Institute of Neurological Disorders and Stroke (NINDS) tissue plasminogen activator (tPA) trial (1995)

Outcome After Thrombolytic Stroke Therapy
Modified Rankin scores at 3 months

- Modified Rankin scores at 3 months in SITS-MOST and randomised controlled trials for placebo and alteplase patients

<table>
<thead>
<tr>
<th></th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>Dead</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pooled placebo 0–3 h (n=465)</td>
<td>14%</td>
<td>15%</td>
<td>11%</td>
<td>15%</td>
<td>20%</td>
<td>8%</td>
<td>17%</td>
</tr>
<tr>
<td>Pooled alteplase 0–3 h (n=463)</td>
<td>19%</td>
<td>23%</td>
<td>7%</td>
<td>14%</td>
<td>12%</td>
<td>7%</td>
<td>18%</td>
</tr>
<tr>
<td>SITS-MOST (n=6,136)</td>
<td>19%</td>
<td>20%</td>
<td>16%</td>
<td>15%</td>
<td>14%</td>
<td>5%</td>
<td>11%</td>
</tr>
</tbody>
</table>

ECASS III

Thrombolysis with alteplase 3 – 4.5 hours post symptom onset

RCT  N=821  Placebo controlled

Median time to administration of treatment = 3hrs 59 minutes

Results:

Favourable outcome associated with alteplase:
OR 1.34 (CI 1.02 – 1.76) p=0.04

No difference in mortality:
7.7% (alteplase) vs 8.4% (placebo)

Increase in symptomatic ICH with alteplase:
2.4% vs 0.2% p=0.008 (only 0.7% fatal ICH)

Conclusion:

Modest but significant improvement in outcome
Acceptable adverse event profile
The third international stroke trial (IST-3) of thrombolysis main results III. Effect of iv thrombolysis with iv rt-PA on death or dependency in the 3035 patients randomised

The IST3 collaborative group - 156 hospitals in UK, Poland, Italy, Sweden, Norway, Australia, Portugal, Belgium, Austria, Switzerland, Canada, Mexico

Disclosures: Boehringer Ingelheim donated rt-PA and placebo for the first 300 patients but had no other part in the study.
Main features of IST - 3

- Prospective, randomised, open study of i.v. rt-PA vs control,
- < 6 h of acute ischaemic stroke
- Primary outcome: the proportion of patients alive and independent at six months
- Randomisation by telephone or internet with minimisation to balance on key prognostic factors
- Baseline & F/U Imaging: CT or MR
  - Blinded central expert panel review of scans
Primary outcome: ‘alive and independent’ (OHS 0-2)

<table>
<thead>
<tr>
<th></th>
<th>rt-PA (n=1515)</th>
<th>control (n=1520)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>554 (37%)</td>
<td>534 (35%)</td>
</tr>
</tbody>
</table>

Absolute difference/1000 = 14 more alive and independent
Fatal & non-fatal intracranial haemorrhage < 7 days

<table>
<thead>
<tr>
<th>rt-PA (n=1515)</th>
<th>Control (n=1520)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>104 (7%)</td>
<td>16 (1%)</td>
</tr>
</tbody>
</table>

P < 0.0001

applying the ‘Cochrane’ definition, of SICH, the 7% IST-3 frequency is comparable with the 7.3% (SITS) registry of 6483 patients treated within licence in routine clinical practice

## Deaths

<table>
<thead>
<tr>
<th></th>
<th>rt-PA (%)</th>
<th>Control (%)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within 7 days</strong></td>
<td>163 (11%)</td>
<td>107 (7%)</td>
<td>↑0.001</td>
</tr>
<tr>
<td><strong>After 7 days, before 6 mo.</strong></td>
<td>244 (16%)</td>
<td>300 (20%)</td>
<td>↓0.009</td>
</tr>
<tr>
<td><strong>All deaths by 6 months.</strong></td>
<td>408 (27%)</td>
<td>407 (27%)</td>
<td>0.6</td>
</tr>
</tbody>
</table>
IST-3 Consistent with Observational Data

- Retrospective analysis of patients undergoing thrombolysis and registered in the Safe Implementation of Treatment in Stroke – International Stroke Thrombolysis Registry (SITS-ISTR) and controls who had not had thrombolysis within the Virtual International Stroke Trials Archive (VISTA)
- Odds of favourable outcome:
  - ≤ 80 years 1.6 (1.5 to 1.7), n = 25 789
  - > 80 years 1.4 (1.3 to 1.6), n = 3439

Mishra et al. Thrombolysis in very elderly people BMJ 2010; 341:c6046
Delay to randomisation and treatment benefit (favourable shift in OHS)*

*Ordinal analysis adjusted for age, baseline NIHSS, and ‘visible ischaemia’
The number needed to treat (NNT)

- 4.5 for 0 to 90 minutes
- 9.0 for 91 to 180 minutes
- 14.1 for 181 to 270 minutes
- 21.4 for 271 to 360 minutes
"The typical patient loses 1.9 million neurons each minute in which stroke is untreated"

Saver, Stroke 2006
Within 3 hours of onset any patient, regardless of age and stroke severity should be considered for thrombolysis.

Within 4.5 hours, patients under the age of 80 should be considered for thrombolysis.

Between 3 and 6 hours decisions about thrombolysis should be made on an individual basis, recognizing that the benefits are likely to be smaller, but that the risks of an adverse outcome, including death will on average not be increased.
Contra-indications

- Definite seizure since stroke onset
- Blood pressure > 180/105 or SBP < 90
- Stroke < 3 months or any ICH
- Surgery or GI / GU bleed < 3 weeks
- Any other recent haemorrhage
- Blood sugar < 2.7 or > 22
- Warfarin with INR > 1.4
- Platelets < 100
Complications
Complications

- Anaphylaxis
- Angio-oedema
- Bleeding (Intracerebral or other)
Bleeding complications

- Symptomatic ICH 6-9% stroke compared to 0.5-0.6% MI thrombolysis
- Usually massive
- Multifocal
- 30 day mortality 60%
Can you predict who will develop intracranial haemorrhage (ICH)?

- Risk scores do not provide reliable predictions for an individual.
- IST-3 analysis of factors that influence:
  - Odds of ICH with rt-PA
  - Odds of benefit from rt-PA
TPA for Cerebral Ischemia within 3 Hours of Onset: Select Changes in Outcome Due to Treatment

Changes in final outcome as a result of treatment:
- Normal or nearly normal
- No major change
- Severely disabled or dead

Early course:
- No early worsening with brain bleeding
- Early worsening with brain bleeding

TPA for Cerebral Ischemia within 3 Hours of Onset: Changes in Final Outcome Due to Treatment

Changes in final outcome as a result of treatment:
- Normal or nearly normal
- Better
- No major change
- Worse
- Severely disabled or dead
Management of SICH

- Stop infusion
- Consider administering 6-8 units cryoprecipitate containing fibrinogen + factor VIII and 6-8 units platelets
- Discuss with neurosurgery and haematology
- Clotting disturbances must be corrected prior to neurosurgery, otherwise manage as for primary ICH
Management of Bleeding

- Use mechanical control where possible – compression venous/arterial puncture sites
- ↑ BP - Intracranial bleed
- ↓ BP, shock - GI/intra-abdominal bleeding
- Transfuse, coagulation tests, surgical opinion
- Delay surgery until fibrinolytic state corrected
Mechanical clot retrieval
Mechanical clot retrieval

- Device: Merci Retriever, the Penumbra System, the Solitaire Flow Restoration Device, and the Trevo Retriever

- Merci and Penumbra devices may increase recanalisation rates in carefully selected patients

- Their clinical utility for improving outcomes after stroke is unproven

- Solitaire and Trevo neurothrombectomy devices achieved significantly higher intracranial large artery recanalisation rates and better patient outcomes
NICE Guidance

- If unsuitable for iv thrombolysis or it has failed
- In patients suitable for thrombolysis only used in the context of research
Current local guideline for Walton Centre

• NIHSS score >12
• MCA (M1) occlusion/Basilar artery occlusion
• Age <80 year
• If there is contraindication to iv thrombolysis or iv thrombolysis has failed
• Within 6 hours onset of symptoms
Stroke thrombolysis in North Wales

• Three site: Wrexham, Glan Clwyd, Bangor

• Stroke team on site: 9am-5pm (Monday to Friday)

• Telemedicine out of hours by 8 on call consultants
Percentage of all stroke admissions thrombolysed in London

- Feb-July 2009: 2.00%
- Feb-July 2010: 12.00%
- Jan-March 2011: 14.00%
- Jan-July 2012: 18.00%
- Jan-March 2013: 19.00%
Risk adjusted mortality by quarter at 90 days in London, Manchester and the Rest of England
Thrombolysis Rates 2012/13 FY

<table>
<thead>
<tr>
<th>Health Board</th>
<th>Thrombolysis Rate</th>
</tr>
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<tbody>
<tr>
<td>ABHB</td>
<td>6.40%</td>
</tr>
<tr>
<td>ABMHB</td>
<td>11.69%</td>
</tr>
<tr>
<td>BCUHB</td>
<td>4.57%</td>
</tr>
<tr>
<td>Cwm Taf</td>
<td>11.61%</td>
</tr>
<tr>
<td>C&amp;V</td>
<td>9.98%</td>
</tr>
<tr>
<td>Hywel Dda</td>
<td>9.91%</td>
</tr>
<tr>
<td>ALL WALES</td>
<td>8.47%</td>
</tr>
</tbody>
</table>

Thrombolysis Rate for Wrexham last one year: 8.9%
Pareto analysis of Reasons for non-thrombolysis YMH July 2013 - Jan 2014
Pareto analysis of non-Thrombolysis reasons, YGC July 2013-Jan 2014

- TimeWindow
- WakeUp
- Mild/Severe
- Haemorrhagic
- OtherMedical
- Age
- Comorbidity
- Improving
- Medication
- Refusal

Number
Cumulative %
AUDIT – STROKE THROMBOLYSIS AWARENESS IN PATIENTS (OR CARER) ADMITTED WITH STROKE IN WREXHAM MAELOR HOSPITAL
DEMOGRAPHICS

• 50 patients
  – 1 x patient allowed patient demographics to be included but refused other data to be included
  – Male – 29
  – Female – 21
  – Age range – 49 – 100 years old
AWARE OF THE FAST CAMPAIGN?

AWARE OF FAST CAMPAIGN?

51% yes
49% no
AWARE OF THROMBOLYSIS?

AWARE OF "CLOT BUSTING MEDICATIONS" THAT CAN BE USED TO TREAT STROKE
**WOULD THE PATIENT HAVE BEEN A CANDIDATE FOR THROMBOLYSIS IF THEY HAD PRESENTED IN TIME?**

<table>
<thead>
<tr>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>23</td>
<td>26</td>
</tr>
</tbody>
</table>

Would the patient have been for thrombolysis if presented in time?
CONCLUSIONS

• The majority of patients/carers appropriately contacted 999 for emergency transfer to A+E (49%)
• Symptom recognition is the major cause of delayed presentation
• Whilst 49% of cases were aware of the National FAST Campaign, only 12 cases were aware that thrombolysis could be used acutely in appropriate ischaemic stroke
• It is possible that by improving symptom recognition and therefore, promoting prompt presentation, the number of successful thrombolysis cases in Wrexham may improve
Door to Needle Time
DTN

Challenge for North Wales!
(Average for Wrexham 79min)
Stroke Thrombolysis Audit

Suhail Hussain, Walee Sayed, Gordon Black, Khwaja Nizamuddin, Sajjad Noor, Lynne Hughes
“Time Lost is Brain Lost”

Systemic thrombolysis represents the only proven therapy for acute ischemic stroke

• Stroke Facts
  • Every minute 1.9 million neurons and 14 billion synapses are destroyed
  • Every hour that treatment is delayed, the ischaemic brain ages 3.6 years
  • Time = Brain
Door to Needle Time

- No current UK guidelines on DTN time in Stroke Thrombolysis

- Recommendations to date have been consistent: DTN <60min
  - American Heart Association/American Stroke Association: Get with the Guidelines®
  - Joint Committee (USA) sets a standard of 80% for DTN <60min

- Sentinel Stroke National Audit Programme (SSNAP)
  Door to needle time for patients receiving thrombolysis with the median time being 59 minutes
Thrombolysis Timings

Minutes

107

79

OTD  DTN
DNT: Working Hours / Out of Hours

Median time in minutes

WH

OOH
DTN: Period

March 12 to Feb 13

- <60 min: 18%
- 60–120 min: 17%
- >120 min: 65%

March 13 to Feb 14

- <60 min: 32%
- 60–120 min: 10%
- >120 min: 58%
Individual Times

- A&E Docs: 41%
- Stroke Docs: 7%
- CT: 45%
- TPA: 7%
CT Scan

![Bar chart showing comparison between WH and OOH in minutes]

- WH
- OOH
Conclusions

• Average Door to needle time 79 min.

• Door to needle times longer out of hours.

• 28% of patients were thrombolysed within 60min of arrival to A&E.

• Twice number of patients were thrombolysed within 60min in second quarter.
Recommendations

- Paramedics: Pre-alert calls for FAST positive.
- AE: arrange CT Head early with clear instruction ‘for thrombolysis’.
- Nursing staff: regular training.
- Radiographer: to prioritise.
Recommendations

• Working hours
  – Stroke Registrar: focussed history and examination
  – Stroke nurse: Patient preparation, monitoring, tPA
  – Stroke consultant: Reviews scan + decision in CT
Recommendations

• Out of hours
  • Medical registrar: thrombolysis & telemedicine training.
    – Stroke Nurse: preparation and time management.
    – Stroke consultant: involve early.
    – Radiographer: more CT training.
Recommendations

- Formal feedbacks: delay, concern
- Formal report: DNT >60 mins with cause of delay
- Monthly thrombolysis Meetings: review feedback, report and consultant recommendation
- Re-audit after 6 months
- One Hyperacute Unit for North Wales
How does the size of a unit influence processes of care?

### Arrival to tPA/scan times

<table>
<thead>
<tr>
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<th>Thrombolysis volume per annum</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0-24</td>
</tr>
<tr>
<td><strong>Median arrival to scan (mins)</strong></td>
<td></td>
</tr>
<tr>
<td>0-24</td>
<td>30 (18-49)</td>
</tr>
<tr>
<td>25-49</td>
<td></td>
</tr>
<tr>
<td>≥ 50</td>
<td></td>
</tr>
<tr>
<td><strong>Median arrival to tPA (mins)</strong></td>
<td></td>
</tr>
<tr>
<td>0-24</td>
<td>78 (57-105)</td>
</tr>
<tr>
<td>25-49</td>
<td></td>
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<tr>
<td>≥ 50</td>
<td></td>
</tr>
<tr>
<td><strong>Arrival to tPA within 1 hour (%)</strong></td>
<td></td>
</tr>
<tr>
<td>0-24</td>
<td>30.4</td>
</tr>
<tr>
<td>25-49</td>
<td></td>
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<tr>
<td>≥ 50</td>
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• Thanks for listening!