Interventions for Acute Ischemic Stroke

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Objectives

1. Discuss the use of IV t-PA and indications for stroke patients

2. Discuss interventions outside of the three hour symptom onset available for stroke patients, including IA t-PA, interventional procedures and surgery
Stroke Epidemiology

• Every year about 795,000 Americans have a new or recurrent stroke
  o Every 40 seconds in the US someone experiences a stroke

• Stroke is the #1 leading cause of disability in the United States
  o Over 5.5 million survivors with >2/3 of them struggling with a range of disabilities

• Stroke is the 5th leading cause of death in the US: about 163,000 deaths/year
  o KY stroke mortality is 10% higher than the national average

• Every 4 minutes someone dies of stroke
The Stroke Belt


Financial Impact

$ Real (2010$) total direct annual stroke-related medical costs = \uparrow \text{ from } $71.55 \text{ billion to } $183.13 \text{ billion}$

$ Real indirect annual costs (lost productivity) = \uparrow \text{ $33.65 \text{ billion to } $56.54 \text{ billion}}$

$ Total annual cost $240.67 \text{ billion by 2030} = \text{ 129% increase!}$

Ovbiagele, et al., 2013
Kentucky Stroke Care Disparities

- Culture
- Education
  - Risk factors
  - Warning signs
  - Treatments
- Geography - Remote locations
- Lifestyle choices - Food choices, low activity level, high smoking rates
- Socio-economic status
- Few stroke-care experts
Types of Stroke

- **Ischemic** 87%
  - Subarachnoid – 3%
  - Intraparenchymal – 10%
- **Hemorrhagic** 13%
- **Other** 4%
- **Cryptogenic** 26%
- **Atherosclerotic** 17%
- **Cardioembolic** 17%
- **Lacunar** 21%


Ischemic Penumbra: Hypo-perfused Area of Focal Ischemia That May Be Salvaged by Timely Intervention

- Infarct: <8 mL/100 g/min
- Penumbra: 8-20 mL/100 g/min
- Normal: 50 mL/100 g/min

Ahmed, 2001
## Estimated Pace of Neural Circuitry Loss in Typical Large Vessel, Supratentorial Acute Ischemic Stroke

<table>
<thead>
<tr>
<th></th>
<th>Neurons Lost</th>
<th>Synapses Lost</th>
<th>Myelinated Fibers Lost</th>
<th>Accelerated Aging</th>
</tr>
</thead>
<tbody>
<tr>
<td>Per Stroke</td>
<td>1.2 billion</td>
<td>8.3 trillion</td>
<td>7140 km/4470 miles</td>
<td>36 y</td>
</tr>
<tr>
<td>Per Hour</td>
<td>120 million</td>
<td>830 billion</td>
<td>714 km/447 miles</td>
<td>3.6 y</td>
</tr>
<tr>
<td>Per Minute</td>
<td>1.9 million</td>
<td>14 billion</td>
<td>12 km/7.5 miles</td>
<td>3.1 wk</td>
</tr>
<tr>
<td>Per Second</td>
<td>32 000</td>
<td>230 million</td>
<td>200 meters/218 yards</td>
<td>8.7 h</td>
</tr>
</tbody>
</table>
Standard of Care:
Treatment Windows from Time Last Known Well

- FDA approved
  - 3 Hours
- IV tPA
  - Evidence-based
  - 4.5 Hours
- Evidence-based
  - 6 Hours
- IA tPA
  - FDA Approved
  - 8 Hours
- Mechanical Retrieval
  - Evidence-based
  - 12 hours
- Mechanical Retrieval

Endovascular intervention may be considered beyond 12 hours
Time is Brain: 2million neurons/minute

Emergency Stroke Alert

• ABCs

• History: **TIME** – last known normal

• Physical Exam: Baseline **NIHSS**

• Imaging: **CT/CTA**
  - CT rules out hemorrhage
  - CTA establishes location of occlusion
  - Perfusion
Frontline Standard of Care

• **IV rt-PA** is the front-line standard of care when criteria met

Class 1; Level of Evidence A, 2013
AHA/ASA Guidelines
Activase Alteplase
A Recombinant Tissue Plasminogen Activator (rt-PA, aka t-PA)

- The only FDA approved thrombolytic agent for treatment of stroke
  - Approved June 1996
- An enzyme which has the property of fibrin-enhanced conversion of plasminogen to plasmin
- Binds to fibrin in a thrombus and converts the entrapped plasminogen to plasmin
- Initiates local fibrinolysis

“Stroke Clot Buster”

Effects of rt-PA vs Time

[Graph showing the effects of rt-PA on stroke outcomes over time]
IV rt-PA

- **3 hours is the FDA approved time window**
  - NINDS Part 1: assessed changes in neurologic deficits 24 hours after the onset
    - No significant change between tPA & control group
  - Part 2 assessed clinical outcomes at 3 months
    - Statistically significant improvement on all 4 stroke scales used
      - NIHSS, Barthel Index, Modified Rankin Scale, GCS
  - Approved 1996

- **4.5 hours is safe and effective in select cases (talk with stroke team)**

- **25% present within 3 hours: 29% eligible**

*IV rt-PA can be given at any hospital, though typically followed by transfer to a primary or comprehensive stroke center*
Efficacy of rt-PA by Stroke Subtype

- **Small vessel**: rt-PA > Placebo
- **Large vessel**: rt-PA > Placebo
- **Cardioembolic**: rt-PA > Placebo
Overall Benefits and Risks of IV rt-PA for Stroke

• Benefit: neurologically normal at 3 months
  o 55% relative increase
  o 12% absolute increase

• Very robust effect: NNT = 8

• Risk of ICH can be reduced by closely following the t-PA protocol (post-admin monitoring)
Current Treatment: IV rt-PA

• Door to Needle goal:
  - < 60 minutes

• Dose: 0.9 mg/kg IV: 10% bolus, remainder over 60 minutes
  - Maximum dose 90mg

• Follow infusion with 50 ml normal saline
  - Clears the line to complete the medication administration
Using rt-PA in Routine Clinical Practice

• Rate of ICH at 36 hours: 4%-6%
  o No increase in 90-day mortality compared to placebo group

• Risk of ICH increases with protocol violations:
  o Time window violations
  o Poor blood pressure control
  o Using prohibited agents
  o Wrong dose
    ▪ Correct = 0.9 mg/kg, Maximum dose: 90 mg
  o Elevated blood sugar also increases risk
Angioedema

- Angioedema: 1-2%
  - More common when on ace inhibitors

Orolingual angioedema can be asymmetric and can occur contralateral to the ischemia.

Assess for ecchymosis that may indicate lingual hematoma.
Indications for IV rt-PA

• Diagnosis of ischemic stroke causing measurable neurological deficit

• Time to treatment less than 3 hours of confirmed time “Last Known Well”
  - 4.5 hours with additional exclusion criteria

• 18 years old or older
Exclusion Criteria for IV rt-PA

- Significant head trauma or prior stroke in previous 3 months
- Symptoms suggest subarachnoid hemorrhage
- Arterial puncture at noncompressible site in previous 7 days
- History of previous intracranial hemorrhage
- Intracranial neoplasm, arteriovenous malformation, or aneurysm
- Recent intracranial or intraspinal surgery
- **Elevated blood pressure (systolic >185 mm Hg or diastolic >110 mm Hg)**
- Active internal bleeding

3 hour time-window
Contraindications/Exclusions

- Acute bleeding diathesis, including but not limited to:
  - Platelets less than 100,000/mm³
  - Heparin received within 48 hours, resulting in abnormally elevated aPTT greater than the upper limit of normal
  - Current use of anticoagulant with INR >1.7 or PT >15 seconds
  - Current use of direct thrombin inhibitors or direct factor Xa inhibitors with elevated sensitive laboratory tests (such as aPTT< INR, platelet count, and ECT; TT; or appropriate factor Xa activity assays)

- Blood glucose concentration <50 mg/dL (2.7 mmol/L)
- CT demonstrates multilobar infarction (hypodensity >1/3 cerebral hemisphere)
Relative Exclusion Criteria:

(Recent experience suggests that under some circumstances—with careful consideration and weighting of risk to benefit—patients may receive fibrinolytic therapy despite 1 or more relative contraindications. Consider risk to benefit of IV rt-PA administration carefully if any of these relative contraindications are present)

• Only minor or rapidly improving stroke symptoms (clearing spontaneously)
• Pregnancy
• Seizure at onset with postictal residual neurological impairments
• Major surgery or serious trauma within previous 14 days
• Recent gastrointestinal or urinary tract hemorrhage (within previous 21 days)
• Recent acute myocardial infarction (within previous 3 months)
Additional Criteria for 3–4.5 hour Window

**Inclusion:**

- Diagnosis of ischemic stroke causing measurable neurological deficit
- Onset of symptoms within 3 – 4.5 hours before beginning treatment

**Exclusion:**

- Aged >80 years
- Severe stroke (NIHSS > 25)
- Taking oral anticoagulant regardless of INR
- History of both diabetes and prior ischemic stroke
30-50% of strokes are large vessel occlusions
Intra-arterial (IA) rt-PA

• Angiograph catheter

• 6 hours
  o **Not** FDA approved
  o Is given based on clinical trial data

• 20-30% recanalization rate
Mechanical Thrombectomy

- Merci Retrieval System®
- Penumbra Retrieval Device
- Solitaire™ FR
- Trevo®

8 hour time-window

12 Hours with ELVO

American Heart Association
American Stroke Association

Norton Healthcare
UKHealthCare

Stroke Care Network
New Designation: ELVO

- Stroke process due to occlusion of ‘large’ vessel

- ANALOGY:
  - STEMI = ST Elevation Myocardial Infarction
  - ELVO = Emergent Large Vessel Occlusion
Large Vessels

- ICA
- A1
- M1
- M2
- Basilar
- Vertebral
ELVO Trials

- MR-CLEAN
- EXTEND-IA
- SWIFT PRIME
- ESCAPE

Halted early for efficacy
Stroke Transfer Protocol

Emergent Large Vessel Occlusion (ELVO)

Clinical Signs of Stroke

Non-contrast Head CT (CTA if Available)

Intracerebral Hemorrhage or Subarachnoid Hemorrhage

Transfer to CSC will automatically accept the patient. Neurosurgery available for phone consultation as needed

No Hemorrhage

Ischemic Stroke Protocol (including IV tPA as appropriate)

Is there an ELVO on CTA or NIHSS ≥ 10? ²

Yes

Symptoms ≤ 12 hours

Continue Stroke Protocol and Immediate Transfer to CSC

No

Symptoms > 12 hours

Continue Stroke Protocol and Consult CSC²

¹ CTA if available and if does not slow workflow
² NIHSS < 10 or symptoms > 12 hours does not preclude transfer
NOTE: The transfer protocol for ELVO should not interfere with current workflow for administration of IV t-PA
Extracranial Angioplasty and Stenting

• Usually for prevention

• Acute Ischemic Stroke:
  o Etiology of stroke is cessation of flow in the extracranial carotid or vertebral artery
    ▪ Atherosclerosis
    ▪ Dissection
  o Catheter access to intracranial thrombus is impeded by extracranial stenosis or occlusion
Decompressive Hemicraniectomy

- Usually large volume or posterior fossa infarctions
- Can reduce mortality from 80% to ~20%
References


5. AHA Statistical Update: Heart Disease and Stroke Statistics—2015 Update: A Report From the American Heart Association, Dariush Mozaffarian, et. al., on behalf of the American Heart Association Statistics Committee and Stroke Statistics Subcommittee, Circulation. 2015;131:e29-e322, published online before print December 17 2014, doi:10.1161/CIR.0000000000000152 http://circ.ahajournals.org/content/131/4/e29.full
