Objectives

Discuss misconceptions associated with the use of alteplase (tPA) in ischemic stroke

Apply the results of recently published trials on the use of endovascular treatment for acute ischemic stroke

Identify novel strategies to decrease door-to-needle and door-to-knife time

Background

All Stroke: 800,000 cases/year

Hemorrhagic: 12%

Ischemic: 88%

Cryptogenic: 30%

Lacunar: 25%

Atherosclerosis: 20%

Hypoperfusion

Arteriogenic emboli

Cardiogenic emboli: 20%

Atrial fibrillation

Valve disease

Ventricular thrombi

Other: 5%

Dissection

Arteritis

Vasospasm

Drug abuse


Types of Imaging

Computed tomography (CT)

- Sequential x-ray slices with reconstruction
- No screening required

CT angiography (CTA)

- Uses iodinated contrast agents to reveal cerebral vasculature
- Timing of contrast can reveal arterial or venous vasculature

Magnetic resonance imaging (MRI)

- Uses magnetic fields and radio waves
- Better anatomical detail, different sequences provide different information
- Patient screening required, increased cost

CT Perfusion

- Can differentiate between ischemic core and penumbra

CT Angiography

Useful for imaging vessels in head and neck

- Carotid stenosis/occlusions
- Vascular structures that preclude endovascular intervention
- Identify large vessel occlusions
- Vascular malformations

Computed Tomography

- Quickly excludes hemorrhage, other stroke mimics
- Can be completed in about 10 minutes
- Low sensitivity for ischemic stroke
- Acute ischemic stroke detected ≤ 67% if within 3 hours from onset
- Arterial occlusion indicative of large clot burden (hyperdense sign)
Magnetic Resonance Imaging

- Multiple sequences useful in acute ischemic stroke (AIS)
  - Diffusion-Weighted Imaging (DWI)/Apparent Diffusion Coefficient (ADC)
  - Fluid-Attenuated Inversion Recovery (FLAIR)
  - Magnetic Resonance Angiograph (MRA)
  - Gradient-Recalled Echo (GRE)

- Can also detect a wider variety of stroke mimics

Sequence Function

- DWI/ADC: Measures Brownian motion of water molecules in extracellular space. Diagnoses AIS within minutes after symptom onset.
- FLAIR: A imaging with fat signal reduced (dark). Identifies AIS 1-3 hours after onset. Helps identify older ischemic strokes and small vessel disease.
- GRE: Detects deoxygenated hemoglobin from extravasated blood. Detects acute or chronic intracranial hemorrhage.

MRI Examples – DWI/ADC and FLAIR

- Left: Left MCA hyperintensity on DWI
- Right: Left MCA hypointensity on ADC

MRI Examples - GRE

- Left: Left-sided intraparenchymal hemorrhage on GRE
- Right: Left-sided intraparenchymal hemorrhage on CT

Interventions for AIS

- Thrombolysis
  - Screening patients
  - Endovascular
  - Bleeding risk

- Failed/ineffective interventions:
  - High dose albumin
  - High dose magnesium
  - Pentoxifylline
  - Glycopyrronium/Ilb/IIIa inhibitors*
  - Early aspirin + tPA
  - Hyperbaric oxygen therapy

Patient Case

A stroke alert within the 3-hour window arrives to the ED. Family states patient does not have any history of coagulopathies, lab abnormalities, or receipt of blood thinners.

- NIH Stroke Score: 8
- 61 year old male
- PMH: hypertension
- Head CT: negative for hemorrhage or any acute intracranial process
- Blood glucose: 140
- Blood pressure: 170/95 mmHg
- No other contraindications to tPA
- Labs (including PT/INR and platelets) are lost, and by the time they are redrawn he will be outside of the window

Would you recommend this patient receive tPA prior to labs being resulted?

IV tPA Contraindications (0 – 3 hour)

- Platelet count < 100,000 mm3
- Hepatitis within last 48 hrs AND INR > ULN
- Anticoagulant use AND INR > 1.7 or PT > 14 sec
- Blood glucose concentration < 50 mg/dL
Necessary labs for IV tPA

- Platelets
- PT/INR
- Blood glucose

Utility of Platelets and INR

- Cucchiara, et al.
  - 5 year retrospective review of AIS patients treated at a single center
  - 1752 patients → 212 with thrombocytopenia → 62 known at time of onset → 5 with history of conditions associated with thrombocytopenia
  - Six (0.3%) had a platelet count < 100k that was unsuspected

- Rost, et al.
  - 5 year retrospective single-center review of AIS patients
  - 2335 patients with AIS → 470 potential for thrombolysis → 30 with INR ≥ 1.7 or platelets < 100k
  - Two (0.4%) had an unsuspected coagulopathy
    - One was due to an elevated INR
    - One was due to decreased platelets

Why do patients bleed after receiving tPA?

- Therapeutic mechanism: cleaving plasminogen to plasmin, which degrades fibrin-based clots

  Bleeding Mechanisms
  - Clot lysis and reperfusion
  - Vasoactivity
  - NMDA excitotoxicity
  - Extracellular proteolysis

Who shouldn’t get IV tPA (4.5 hour +)?

- 3-4.5 hr window: Everything in the 0-3 hr window AND
  - Aged >80 years
  - Severe stroke (NIHSS>25)
  - Any oral anticoagulant regardless of INR
  - History of diabetes AND prior ischemic stroke
  - Concern for proximal MCA occlusion → more likely to benefit from endovascular treatment
- 4.5-6 hr window: pretty much everybody

Risk factors for Intracranial Hemorrhage (ICH) post-tPA

- Age
- Blood glucose
- Prestroke modified Rankin Score (mRS)
- Hypertensive MCA sign
- Time from onset to treatment
- Admission NIHSS
- History of hypertension
- History of diabetes mellitus
- Weight
- Early CT infarct
- Weight
- Thrombocytopenia
- Admission systolic blood pressure
Clinical Scores for Prediction of ICH/Outcome

Clinical Score | Components
---|---
**Stroke-TPI** | Age, NIHSS, blood glucose
**DRAGON** | Age, prestroke NIHSS, hyperdense MCA infarct or early CT infarct, blood glucose, onset to treatment time, admission NIHSS
**Skan-100** | Age, admission NIHSS
**ASTRAL** | Age, admission NIHSS, onset to treatment time, GCS, visual field defects, glucose
**M5S** | Age, admission NIHSS, glucose, platelets
**HAT** | DM or glucose, admission NIHSS, early CT hypodensity
**SESDAN** | Age, NIHSS, glucose, HDMCA sign, early CT infarct
**SITS-ICH** | Age, weight, hypertension, Aspirin/Clopidogrel, admission NIHSS, systolic BP, glucose, onset to treatment time

Clinical Scores Compared

| Score | ODDS ratio (95% CI) | Z statistic | P value | Hosmer-Lemeshow χ² | df | Groups | P value | IRC (area 95% CI) |
|---|---|---|---|---|---|---|---|---|---|
| M5S | 1.99 (1.01 - 3.92) | 3.3 | 0.042 | 2.8 | 7 | 0.03 | 0.6 | 0.03 | 0.03 (0.01, 0.06) |
| SAVER-3 | 1.99 (1.01 - 3.66) | 2.04 | 0.046 | 0 | 10 | 0.43 | 0.17 | 0.43 (0.17, 0.80) |
| ASTRAL | 1.99 (1.01 - 3.92) | 2.56 | 0.011 | 0.01 | 8 | 0.08 | 0.08 | 0.08 (0.04, 0.12) |
| HAT | 1.99 (1.01 - 3.92) | 2.93 | 0.004 | 5.14 | 8 | 0.24 | 0.24 | 0.24 (0.09, 0.60) |
| PRES | 1.99 (1.01 - 3.92) | 1.99 | 0.046 | 0.17 | 6 | 0.05 | 0.05 | 0.05 (0.01, 0.17) |
| SITS-ICH | 1.99 (1.01 - 3.92) | 2.17 | 0.034 | 5.13 | 5 | 0.17 | 0.17 | 0.17 (0.06, 0.48) |
| SITS-MIR | 1.99 (1.01 - 3.92) | 1.85 | 0.12 | 7.79 | 7 | 0.08 | 0.08 | 0.08 (0.04, 0.12) |
| SITS-MIR-HEM | 1.99 (1.01 - 3.92) | 1.87 | 0.12 | 7.79 | 7 | 0.08 | 0.08 | 0.08 (0.04, 0.12) |

Grey: percent likelihood of good outcome (mRS = 0 - 2)
Blue: percent likelihood of miserable outcome (mRS = 5 - 6)

Hemorrhage After Thrombolysis (HAT)

<table>
<thead>
<tr>
<th>Scoring</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Presence of diabetes mellitus or admission blood glucose = 200 mg/dL</td>
<td>1</td>
</tr>
<tr>
<td>Pretreatment NIHSS</td>
<td>15 - 30</td>
</tr>
<tr>
<td>Baseline NIHSS</td>
<td>&gt;30</td>
</tr>
<tr>
<td>Presence of easily visible hypo-densities on initial CT</td>
<td>0.4/3 MCA territory</td>
</tr>
<tr>
<td></td>
<td>&gt;0.4/3 MCA territory</td>
</tr>
</tbody>
</table>

Risk of ICH in Stroke Mimics and Mild AIS

- **Stroke mimics:**
  - Examples: hypo/hyperglycemia, seizures, multiple sclerosis, hemiplegic migraine, psychiatric conditions, intracranial infections or tumors
  - Only 52-72% of prehospital stroke alerts are diagnosed by an MD as an acute ischemic stroke
  - Significant risk of misdiagnosis and subsequent treatment
  - Mild ischemic strokes (NIHSS < 5)
    - Lower benefit, same risk?

Symptomatic ICH in Mild AIS

- Retrospective analysis of 5,910 patients treated with tPA within 4.5 hours of onset
- Stratified by treatment window (0 - 3 hours vs. 3 - 4.5 hours)
- Overall incidence of symptomatic ICH (sICH): 1.8%
  - No difference based on treatment window
  - Association with increased age (OR = 1.35), carotid stenosis (OR = 2.35), altered consciousness (OR = 2.70), care in stroke unit (OR = 0.57), and dyslipidemia (OR = 0.62)
Symptomatic ICH in Stroke Mimics

- Prospective cohort study of patients at a tertiary care center + meta-analysis comparing stroke mimics (SM) to AIS over 5 years – 75 SM compared to 441 confirmed AIS – Incidence of sICH similar between groups (1.3% vs. 1.13%)
- Meta analysis compared 392 SM to 8085 confirmed AIS – Incidence of sICH only 0.5% compared to 5.2% in confirmed AIS – Similar to rates of patients receiving placebo in NINDS studies

Rates of Spontaneous ICH

<table>
<thead>
<tr>
<th>Patient Population</th>
<th>% (95% CI)</th>
<th>No. of Patients</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA (0.9 mg/kg)</td>
<td>7.0% (5.2%–8.7%)</td>
<td>2450</td>
<td></td>
</tr>
<tr>
<td>IA tPA</td>
<td>9.3% (6.0%–12.7%)</td>
<td>1143</td>
<td></td>
</tr>
<tr>
<td>Mechanical removal alone</td>
<td>7.8% (2.2%–8.4%)</td>
<td>90</td>
<td></td>
</tr>
<tr>
<td>IA tPA + Mechanical</td>
<td>9.3% (6.5%–11.1%)</td>
<td>819</td>
<td></td>
</tr>
<tr>
<td>0.6 mg/kg IV tPA + IA tPA</td>
<td>0.0% (2.0%–11.0%)</td>
<td>292</td>
<td></td>
</tr>
<tr>
<td>0.9 mg/kg IV tPA + IA tPA</td>
<td>0.0% (0.7%–10.4%)</td>
<td>224</td>
<td></td>
</tr>
<tr>
<td>Mild Stroke (NIHSS &lt; 5)</td>
<td>1.8%</td>
<td>5910</td>
<td>GWTS Registry</td>
</tr>
<tr>
<td>Stroke Mimics</td>
<td>0.5% (0%–2%)</td>
<td>392</td>
<td>High volume stroke center + MA</td>
</tr>
</tbody>
</table>

Interventions for AIS

Thrombolysis
- Screening Patients
  - Platelets and INR have limited utility in detecting unknown coagulopathies prior to thrombolysis
  - Estimating bleeding risk
  - Clinical scores such as HAT and DRAGON can help predict ICH and outcome after thrombolysis prior to administration
  - Risk of ICH after thrombolysis in stroke mimics and mild ischemic stroke is low

Endovascular
- Mechanisms of action
- Road to clinical relevance

Types of Endovascular Interventions

What is endovascular?

- Merici: https://youtu.be/7yn96se600I?t=29
- Penumbra: https://youtu.be/lyfZNeRO0k?t=35
- Solitaire: https://youtu.be/0DQPD5TTSSY?t=16

Previous recommendations

- Although the MERCI device is a reasonable intervention for extraction of intra-arterial thrombi in carefully selected patients, the panel also recognizes that the utility of the device in improving outcomes after stroke is unclear (Class IIIb, Level of Evidence C).
- The panel also recommends that the device be studied in additional clinical trials that will define its role in the emergency management of stroke. The usefulness of other mechanical endovascular treatments is not established (Class IIIb, Level of Evidence B).
- These devices should be used in the setting of clinical trials.
Earlier Endovascular Trials

- IMS III (2013)
  - IV tPA within 3 hours +/− endovascular treatment (ET) within 5 hours
  - Stopped for futility at 636 of 900 enrolled patients
  - No difference in uCH, modified Rankin Score (mRS) at 90 days
- SYNTHESIS Expansion (2013)
- IV tPA +/− intervention both within 4.5 hours
- IV tPA received significantly faster than ET (2.45 vs. 3.45, p<0.001)
- MR RESCUE (2013)
- ET within 8 hours had no effect on patients with favorable penumbral pattern (mean mRS, 3.9 vs. 3.4; p=0.23)

New Endovascular Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Control (n)</th>
<th>Intervention (n)</th>
<th>Primary Outcome</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>EXTEND-IA</td>
<td>IA + IA tPA (165)</td>
<td>MT + IA tPA (35)</td>
<td>30-day functional independence (mRS ≤ 2)</td>
<td>p=0.002</td>
</tr>
<tr>
<td>MR CLEAN</td>
<td>Usual care (267)</td>
<td>IA + IA tPA (98)</td>
<td>30-day functional independence (mRS ≤ 2)</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>ENACTE</td>
<td>Usual care (103)</td>
<td>IA + IA tPA (98)</td>
<td>30-day mortality</td>
<td>p=0.002</td>
</tr>
<tr>
<td>SWIFT PRIME</td>
<td>IA (58)</td>
<td>IA + IA tPA (98)</td>
<td>30-day median mRS</td>
<td>p=0.002</td>
</tr>
</tbody>
</table>

Pharmacist’s Role

- More intensive screening
  - Assist in determining eligibility for tPA
- Risk of contrast-induced nephropathy?
  - No increased risk of requiring emergent dialysis
  - OR=0.96, 95% CI 0.54-1.60
  - No increased risk for short term mortality
  - OR=0.87, 95% CI 0.87-1.06
  - Compare to up to twice the rate of function independence with ET

Stroke Regulations

- CMS/TJC
  - STK-4: Acute ischemic stroke patients who arrive at this hospital within 2 hours of time last known well and for whom IV t-PA was initiated at this hospital within 3 hours of time last known well.
  - Same priority as trauma, acute MI
  - What about door to needle (groin puncture)?

UF Health Workflow

- Addition of endovascular treatment a significant increase in workload for:
  - Neurology
  - ED staff
  - Radiology staff
  - Interventional Radiology/Neuro-endovascular

Stroke Emergency Mobile (STEMO)

- Neurologist
- Paramedic
- Radiology technician
- CT scanner
- Laboratory
  - CBC, BMP, INR
- Neuroradiologist on call
- Can give tPA en route
- Hours: 7AM – 11PM
**STEMO Methods**

- Randomized, open-label trial over 21 months in 2011-2013
- Compared standard of care to STEMO in 4 week blocks in Berlin, Germany
  - STEMO → control → STEMO → control
- Included patients with Last Known Well (LKW) within 4 hours
  - > 18 years, not pregnant
- tPA given within 4.5 hrs from LKW per European guidelines
- Primary: duration from activation to tPA bolus
  - Safety: death within 7 days

**Target: Stroke**

- AHA-sponsored, evidence-based quality improvement program
- Launched in January 2010 to increase percentage of patients that receive timely tPA administration
  - Goal door to needle (DTN) < 60 minutes

**STEMO Results**

- 6182 patients enrolled: 3213 to STEMO, 2969 to control
  - STEMO could not reach 1409 patients due to already being in use

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Receiving STEMO</th>
<th>Control (4560)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of tPA treatment, (%) (95% CI)</td>
<td>32.4%</td>
<td>21.3%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Door to treatment time, mean (95% CI)</td>
<td>102.7 min (91.9-113.5)</td>
<td>118.5 min (111.8-125.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Intravascular complications, (%) (95% CI)</td>
<td>3.3% (1.7-7.7)</td>
<td>6.4% (3.8-10.4)</td>
<td>0.18</td>
</tr>
<tr>
<td>Deaths within 7 d, (%) (95% CI)</td>
<td>9.5% (2.4-6.8)</td>
<td>6.5% (2.5-8.2)</td>
<td>0.09</td>
</tr>
</tbody>
</table>

**Target: Stroke Components**

- Advance hospital notification by EMS
- Rapid triage, protocol and stroke team notification
- Single-call activation system
- Stroke assessment tools
- Rapid acquisition and interpretation of brain imaging
- Rapid laboratory testing
- Mix tPA medication ahead of time
- Rapid access to intravenous tPA
- Team-based approach
- Prompt data feedback

**Target: Stroke – Methods**

- 1,030 hospitals in GetWith the Guidelines registry
- 71,169 patients received tPA within 3 hours

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Preintervention (27,329)</th>
<th>Preintervention (45,490)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV DTN time, median (IQR)</td>
<td>77 min (60-96)</td>
<td>87 min (51-87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>IV DTN time ≤ 60 min, % (95% CI)</td>
<td>26.5% (26.0-27.1)</td>
<td>43.3% (40.8-47.1)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>End of period</td>
<td>29.6% (27.8-31.5)</td>
<td>53.3% (51.5-55.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% improvement/year</td>
<td>1.39 (1.04-1.67)</td>
<td>6.30 (5.58-7.08)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>In-hospital mortality</td>
<td>9.93%</td>
<td>8.22%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Discharge to home</td>
<td>37.6%</td>
<td>42.7%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>1.08%</td>
<td>6.69%</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

**Target: Stroke – Phase II**

- Advance hospital notification by EMS
- Rapid triage, protocol and stroke team notification
- Single-call activation system
- Stroke assessment tools
- Rapid acquisition and interpretation of brain imaging
- Rapid laboratory testing
- Mix tPA medication ahead of time
- Rapid access to intravenous tPA
- Team-based approach
- Prompt data feedback

[www.targetstroke.org](http://www.targetstroke.org)
Quality Improvement

- Observer effect – productivity increases when participants know they are being studied
- Process Improvement Methodologies
  - Total Quality Management/Continuous Quality Improvement
  - Plan Do Study Act
  - Six Sigma
  - Lean
  - Lean Six Sigma

Six Sigma

- Originated at Motorola, popularized by GE
  - Voice of the Customer (patient)
  - Voice of the Process
- All work is part of a system/process
- Every process has variation, typically not that which comes from a patient, that which the health care system creates for itself
- All variation can be reduced (not eliminated)
- DMAIC – Define, Measure, Analyze, Improve and Control

Lean Production System

- Developed and still used by Toyota
- Driven by identification of customer needs and removal of waste

Lean Six Sigma

- Combination of Six Sigma and Lean Production Systems
- Applies DMAIC to identification and elimination of waste
- Categories of waste:
  - Downtime
  - Overproduction
  - Waiting
  - Non-utilized talent
  - Transportation
  - Inventory
  - Motion
  - Extra Processing

Waste in Medication Administration

- Over/Underdose
- Transport
- Motion
- Defects
  - Inventory
  - People
  - Downtime
  - Overtesting

Application: tPA Administration

1. tPA order placed
2. tPA order verified
3. tPA removed from med cabinet
4. IV tubing retrieved from supply cabinet
5. tPA reconstituted
6. tPA bottle spiked with IV tubing
7. tPA bolus removed from bottle
8. IV pump readied and programmed
9. IV tubing attached to patient line
10. tPA bolus given to patient
11. tPA infusion started
12. Saline bag hung to flush line
### Application: tPA Administration

1. tPA order placed
2. tPA order verified
3. Bundle of tPA, tubing removed from med cabinet
4. tPA reconstituted
5. tPA bottle spiked with IV tubing
6. tPA bolus removed from bottle
7. tPA waste removed from bottle
8. IV pump readied and programmed
9. IV tubing attached to patient line
10. tPA bolus given to patient
11. tPA infusion started
12. Saline bag hung to flush line

**Key:**
- MD task
- RN task
- PharmD task

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### Treatment Options in the New Endovascular Era & Controversies in Acute Ischemic Stroke

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