Critical Care Management of Acute Ischemic Stroke
Nerissa U. Ko, MD, MAS
Professor of Neurology
May 29, 2014

Overview
- Pathophysiology of focal ischemia
- Role of acute revascularization
- Acute emergency care
- Blood pressure management
- Post-stroke cerebral edema
- ICU care after stroke

Pathophysiology
- Time dependent
- Focal ischemia is different from global ischemia
- Energy failure -> Ca++ entry and cell death
- Glutamate toxicity
- Apoptosis

Disclosures
- Nothing to disclose

Selected slides courtesy of Wade Smith, MD, PhD
Role of Time – IV rtPA
Most Recent Pooled Analysis of IV rtPA Trials

- NINDS Part 1
- NINDS Part 2
- ATLANTIS A
- ATLANTIS B
- ECASS II
- ECASS III
- EPITHET

Lees et al., Lancet, 2010

Revascularization Therapy with IV tPA

- Tissue plasminogen activator (t-PA)
  - IV t-PA is approved in US for AIS within 3 hours of symptom onset (OR 1.9; 95% CI 1.2-2.9)
  - 3 to 4.5 hour window is effective (ECASS-III)

ECASS-III

- Bleeding
  - 6.4% vs. 0.6% in clinical trials
  - no mortality difference
  - Registry data shows improve safety (1.6% bleeding rate)
  - Increased risk if not adhering to NINDS trial protocol
  - Earlier treatment associated with better outcomes, less complications

- Angioedema (1.3-5.1%)
  - Swelling of lips, tongue self limited
  - Rx: IV ranitidine, diphenhydramine, methylprednisolone

Complications with IV tPA

- Treatment of tPA-related bleeding ‘preserve fibrin’
  - 10 units cryoprecipitate
  - Aminocaproic acid
    - 4.5 gm IV, diluted in 250 mL of D5W or NS, infuse over 1 hr, followed by 1 g/hr (50 mL/hr) for about 8 hr or until bleeding is controlled
  - Tranexamic acid
    - 15 mg/kg IV followed by an infusion of 1 mg/kg/hr for 5-6 hours
    - 2 units FFP
    - 10 units platelets
    - Blood transfusion
    - PCC, Factor VIIa ??

- Post-MI myocardial rupture (rare)
Revascularization without IV tPA

- **IA Lytics**
  - PROACT-II trial supports benefit from IA pro-urokinase; t-PA is used off label

- **Mechanical Embolectomy**
  - Devices do open vessels and have FDA clearance to open vessels
  - 2 ongoing, 1 completed study to establish clinical efficacy (MERCI, PENUMBRA, IMS-3)
  - Stent retriever trials: Solitaire and Trevo (SWIFT, TREVO) show improved efficacy

Acute stroke interventions

<table>
<thead>
<tr>
<th>Time from stroke symptom onset (hr)</th>
<th>IV t-PA</th>
<th>Thrombectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 to 3</td>
<td>Proven Approved</td>
<td>Unproven</td>
</tr>
<tr>
<td>3 to 6</td>
<td>IA pro-UK</td>
<td>Proven Unapproved</td>
</tr>
<tr>
<td>6 to 8</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Rescue therapy after IV tPA

**The NEW ENGLAND JOURNAL OF MEDICINE**

Endovascular Therapy after Intravenous t-PA versus t-PA Alone for Stroke

Broderick, J. C., et al. NEJM, March 2013

Interventional Management of Stroke (IMS-III)

- NIH sponsored, randomized, prospective trial of IV t-PA vs. IV t-PA + endovascular

<table>
<thead>
<tr>
<th>656</th>
<th>Stroke</th>
<th>IV t-PA</th>
<th>434</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CT No.</td>
<td>t-PA</td>
<td>222</td>
</tr>
<tr>
<td>58 study centers</td>
<td>6 years</td>
<td>Finish t-PA</td>
<td>Outcome: 90-Day mRS</td>
</tr>
</tbody>
</table>

Broderick et al., NEJM, March 2013
Broderick et al., NEJM, March 2013

- IV tPA
  - Proven efficacy
  - Better outcome earlier in all subgroups
- IA lytics
  - Proven efficacy
  - Unapproved for IA tPA
  - Earlier is better, <6 hours
- Embolectomy
  - Stent retrievers better
  - Solitaire, Trevo, Merci Penumbra all able to recanalize vessels
  - No clinical efficacy data
- Recue therapy
  - New trial data no benefit
  - Ongoing trials with new devices (SWIFT-PRIME)
  - Better selection and improved timing

Stroke Revascularization 2014

- IV tPA
- IA lytics
- Embolectomy
- Recue therapy

CTA shows BA, ICA-T, M1 or M2 Occlusion

IV t-PA + Endovascular   Endovascular   Image Guided Endo

0 hours 3 4.5 6 8 12

Stroke CT Obtained   Ischemic Stroke   IV t-PA Eligible?   IV t-PA

Large Vessel Occlusion?   Yes   Yes   Yes

Embolectomy / IA lytics   Medical Therapy

Hemorrhage   Treat Cause

911: Paramedics Arrive

Transport to UCSF Call Ahead to ED

Patient Arrives in ED:
- Stroke Pager Called
- Stroke CT ordered
- Labs drawn
- Family located

911; Paramedics Arrive

Transport to UCSF Call Ahead to ED

Patient Arrives in ED:
- Stroke Pager Called
- Stroke CT ordered
- Labs drawn
- Family located
Acute supportive care post stroke

- Airway, ventilation, oxygenation
  - Common saturation <96%
  - Especially with underlying cardiac, pulmonary disease
  - Airway obstruction, aspiration, atelectasis, pneumonia
  - Hypoventilation, Cheyne–Stokes
- To intubate or not??
  - Poor outcome in >50% at 30 days

- Cardiac monitoring
  - 24 hours continuous for Afib and other rhythms
  - In cryptogenic stroke, cardiac event monitors
- Hypotension
- Hypovolemia
- Hyperthermia
- Hypoglycemia

HTN after Acute Stroke

- Acute HTN is common after acute stroke
- Current guidelines suggest treatment for SBP > 220 mmHg or DBP > 120 mmHg or if evidence of end-organ damage
- With thrombolytic therapy, goal BP < 180/105 mmHg
- Risk of acute deterioration with aggressive reduction of BP
- Blood pressure reduction within 24 hours is associated with poor outcome
  - OR 1.89 per 10% decrease (p= 0.047) of poor outcome at 3 months

*Neurology 2000; 61:1047-51*
Blood pressure goals

- Optimal blood pressure after acute stroke is controversial
- Treat blood pressure cautiously in acute ischemic stroke
  - t-PA limit <185/110 mmHg
  - Lower BP by 15% if exceeds 220/120 mmHg
- Choice of BP agent is controversial
  - Labetolol and nicardipine don’t raise ICP
- Awaiting new trial data: ENOS, ENCHANTED

Hubert, et al., International J Hypertension, 2013

Ischemic Stroke Penumbra


**Induced Hypertension**

- Remains experimental
- Consider in specific cases
  - Hypotension unresponsive to fluid resuscitation
  - Fluctuating neurological symptoms with hemodynamic changes
  - Increase BP by 10-20% using pressors and observe for symptom resolution
  - Potential to incorporate perfusion imaging

**Volume expansion/Hemodilution**

- Volume expansion with Dextran, hetastarch, albumin
- No benefit in meta-analysis
- ALIAS: High dose albumin trial stopped
- Awaiting trial data
- Treatment of hypotension with isotonic fluids and pressors
- Devices to augment BP with counterpulsation in trials only
- Vasodilators and hemodilution not recommended

**Cerebral Edema**

- Severe, life-threatening complication after acute ischemic stroke
- Occurs in 10-20% of anterior circulation strokes
  - Carries a 50-80% mortality when associated with distal carotid or proximal MCA occlusion
- Posterior fossa strokes can present with hydrocephalus and brainstem compression
  - Should be treated with early suboccipital decompression if brainstem is compressed

**Malignant infarct**

- Small infarct
Malignant Cerebral Edema

- Typically pattern occurs 3-5 days post-infarct, and generally subsides in 2 weeks
- Rarely, edema can occur within 24 hours with signs of early herniation
- Difficult to predict which patients are at risk
  - Evidence of >50% MCA infarct within 12 hours
  - Early sulcal effacement and midline shift
  - Reperfusion injury after thrombolysis
  - Perfusion maps potentially helpful; DEFUSE study

Medical Management

- HOB 30 degrees
- Hyperventilation
  - Goal pCO2 25-30 mmHg
  - Transient, temporizing measure
- Hyperosmolar therapy
  - Mannitol
  - Hypertonic saline
- Hypothermia (33-34 degrees Celsius)
- No role for corticosteroids

Osmolar Therapy

- Mannitol
  - Typically bolus over 20 min (0.25-0.5 g/kg every 4-6 hours)
  - Monitor for hypotension and hypovolemia
  - Can precipitate renal failure
  - Less effective at serum osms >320 mmol/dl
- Hypertonic saline
  - Infusion of 3% NaCl to maintain serum sodium gradient
  - Bolus of 23.4% NaCl over 20 minutes very effective
  - Less side effects of hypotension, renal failure
Hemicraniectomy in Ischemic Stroke

- Decompressive surgery to decrease mass effect and tissue shift after ischemia is controversial.
- Evidence of benefit in patient populations such as trauma, SDH, mass lesions and posterior fossa strokes.
- Meta-analysis showed reduced mortality and improved outcomes with hemicraniectomy for hemispheric strokes.

European Pooled Trial

- Prospective pooled analysis of 3 trials of decompressive surgery in malignant MCA infarction.
- DECIMAL, DESTINY, HAMLET
  - Age 18-60
  - Treatment initiated within 48 hrs of stroke onset
  - Randomized to surgery or conservative Rx
  - N=93 patients
  - Reduced mortality 78-29%

### Results

- Alive but unable to walk (NNT=2)
- Alive, disabled but able to walk (NNT=4)
- Side of stroke (dominant hemisphere)
- Did not matter

---

**Hemicraniectomy in older patients**

- Randomized 112 subjects age 61-82 within 48hrs of MCA stroke
- Increased survival and decreased severe disability
- Survivors required assistance with ADLs

---

**General ICU Care**

- **Airway**
  - Afib 24 hours
- **Temperature**
  - Treat fever with antipyretics
  - Cooling blankets, endovascular treatments not proven to change outcome
  - Hypothermia is experimental at present
- **Infection**
  - No antibiotic prophylaxis, but early treatment
  - Avoid foley catheters
Glucose management

- Glucose
  - Treat hypoglycemia (glucose <60 mg/dl) immediately
  - Keep serum glucose 140-180 mg/dL
  - Infusion vs. sliding scale insulin is controversial

SHINE
Stroke Hyperglycemia Insulin Network Effort

Nutrition

- Assess and document swallowing EARLY
- Discourage rule of NPO X 24 hour as a standard
- NG tube is preferred if swallowing is unsafe
- Start feeds as soon as possible

DVT prophylaxis

- 10% PE related deaths
- Compression devices unless DVT present
- Both SQ unfractioned heparin and LMWH are safe and effective to prevent venous clot and likely PE
- PREVAIL trial favors LMWH over heparin SQ
- Early mobilization: AVERT trial within 24 hours


Palliative care

Palliative and End-of-Life Care in Stroke: A Statement for Healthcare Professionals From the American Heart Association/American Stroke Association


*Stroke*. published online March 27, 2014;
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2014 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628
World Wide Web at: http://stroke.ahajournals.org
The online version of this article, along with updated information and services, is located on the
http://stroke.ahajournals.org/subscriptions/
Subscriptions:
http://www.lww.com/reprints
Information about reprints can be found online at:
Reprints:
Permissions:
Permissions and Rights Question and Answer process is available in the
Request Permissions in the middle column of the Web page under Services. Further information about this
Requests for permissions to reproduce figures, tables, or portions of articles originally published
Permissions:
Stroke Centers

- System approach for stroke shown to improve outcomes
- Pre-printed orders, leadership, QA, connection to community/EMS
- JC accreditation and auditing
- Comprehensive stroke centers with endovascular capability certification started

Guidelines

Stroke

BP trials

- CHHIPS: labetalol and lisinopril
- SCAST: candesartan may be harmful
- CATIS:
- INWEST: worse outcomes with IV nimodipine
- COSSACS: initiation of BP meds with better outcomes
- Higher BPs benefited from lowering, better early, not clearly harmful. No specific agent
Antithrombotic Therapy for Stroke

Antithrombotic agents

- Avoid routine use of IV heparin, IIb/IIIa agents
- Aspirin alone is the only proven strategy within the first 24-48 hours
- Dural sinus thrombosis and arterial dissection may specifically benefit from heparin

Secondary Prevention

- Antiplatelet
  - ASA within 24-48 hours of onset
  - Clopidogrel or asa+persantine first line by discharge
- Anticoagulants
  - Warfarin for atrial fibrillation
  - Target specific oral anticoagulants: dabigatran, rivaroxiban, apixiban

Low molecular weight heparin

- LMWHs and heparinoids reduce the risk of venous thromboembolic events
  - DVT OR 0.27 (CI 0.08-0.96)
  - PE OR 0.34 (CI 0.17-0.69)
- No significant reduction in death and disability OR 0.87 (CI 0.72-1.06)
- Significant increase in major systemic hemorrhages (OR 2.17) but not ICH (OR 1.7)
Induced Hypertension

For
- May increase pial-pial blood flow
- Increase perfusion to the ischemic penumbra
- Is probably safe

Against
- Requires ICU care and central line access
- May cause coronary or gut ischemia
- Could cause cerebral vasoconstriction

Induced Hypertension is Safe

- Retrospective safety study in acute stroke patents
  - 33 controls vs. 30 treated with neosynephrine
  - 10/30 treated patients had BP threshold
  - No increased cardiac morbidity

Evidence for Induced Hypertension

- Koenig, et al. (2006)
  - 100 patients randomized to either induced HTN or standard therapy
  - Used perfusion MRI to select patients with ischemic penumbra (mismatch DWI/PWI)
  - Non-significant decrease in NINDS scores at discharge in treated group, but with longer LOS, ICU time
  - No difference in adverse events