NEUROCRITICAL CARE MANAGEMENT OF ISCHEMIC STROKE

Sanjeev Sivakumar, M.D.
Clinical Assistant Professor, USC - Greenville School of Medicine
Greenville Health System
CRITICAL CARE MANAGEMENT OF ACUTE ISCHEMIC STROKE

Initial Stabilization and routine ICU issues

- Airway and ventilation
- Hemodynamic, cardiac, and fluid status
- Temperature and glucose
- Seizures
- Anemia and transfusion
- VTE prevention and treatment
- End-of-life care, organ donation

Specific Issues

- Unstable (perfusion dependent) exam
- Hemodynamic optimization
- Complications from reperfusion
  - Orolingual angioedema from r-tPA
  - Hemorrhagic conversion
- Cerebral edema, brain herniation
- Surgery in AIS
Clinical Scenario

- 60 yo male with h/o HTN, prior TIA (unknown symptoms)
- LSW 8 PM; found unresponsive at home by wife 11PM
- NIHSS: Initially 17; 21 during telestroke evaluation for R hemiplegia and global aphasia
- Initial Vitals: BP 160/90s, HR 90s
- No contraindications for tPA
- IV tPA at 11:55 PM (3hrs:55 min from LSW)
  → Medflight for possible MER
- Exam on transfer to our ED: NIHSS 23
- Intubated for respiratory distress
- New onset Atrial fibrillation
IA deferred due to large L MCA stroke with poor collaterals
Background

- 15-20% of Acute Ischemic Stroke patients get admitted in ICUs
- Comprehensive stroke center requires presence of “an intensive care unit for complex stroke patients that includes staff and licensed independent practitioners with expertise and experience to provide neurocritical care.”

- The Joint Commission, 2011
Background

- Common indications for intensive care
  - Risk/presence of hemorrhagic transformation
  - Risk/presence of significant cerebral edema
  - Intubation due to brainstem stroke/compression
  - Hemodynamic instability (e.g. Afib w/RVR, MI)
  - Post-procedure, post-surgical care
Perfusion dependent exam: Principals

- Ischemic core and Penumbra
- Importance of collateral flow
- Induced hypertension
Ischemic Penumbra
DWI/PWI Mismatch

- CBF < ~10-12 ml/100g/min
- Diffusion abnormality
- Cytotoxic edema
- Irreversible Ischemia

- CBF 12-18 ml/100g/min
- Isoelectric EEG
- Loss of evoked potentials
- Perfusion abnormality
- Reversible Ischemia
(a) PCOM
(b) Leptomeningeal anastomoses between ACA and MCA
(c) Leptomeningeal anastomoses between PCA and MCA
(d) Tectal plexus between PCA and SCA
(e) Anastomoses of distal cerebellar arteries
(f) ACOM

Carotid I’s L’s T’s: Collaterals shape outcomes of Intracranial carotid occlusion in acute ischemic stroke
Collateral Flow
Collateral Flow
Collateral Flow
Collateral Flow
Collateral Flow

Collateral Flow
Intrinsic Autoregulation
Vasodilatory Response
Hemodynamic Optimization

- Approximately 85% AIS patients are hypertensive (SBP>140 mmHg) on presentation
- Both very high and very low BP are deleterious
- Mild/ relative hypotension can be associated with larger stroke volume
- BP declines spontaneously over the first week to pre-stroke levels in two-thirds
- “U” shaped relationship between blood pressure and Outcomes
Effects of Immediate Blood Pressure Reduction on Death and Major Disability in Patients With Acute Ischemic Stroke

The CATIS Randomized Clinical Trial

- Single-blind, RCT
- 4071 Non-thrombolysed AIS patients within 48 hours of onset
- Treatment: ↓SBP by 10%-25% within the first 24 hours after randomization, achieving blood pressure less than 140/90 mm Hg within 7 days, and maintaining this level during hospitalization
- Control: Discontinue all antihypertensive medications during hospitalization
- Primary outcome: Death + mRS ≥3 at 14d or discharge
- Mean 24H reduction in SBP (−12.7%) Vs. (−7.2%) [95%CI −10.2 −8.1; \( P<0.001 \)]
- Mean 7D SBP 137.3 Vs. 146.5 mm Hg [95%CI −10.1 to −8.4; \( P < .001 \)]
- Primary outcome: OR 1.00 [95% CI, 0.88 to 1.14]; \( P=0.98 \)
- 3month outcomes: OR 0.99 [95% CI, 0.86 to 1.15]; \( P = 0.93 \)

doi:10.1001/jama.2013.282543
Figure 3. Effect of Antihypertensive Treatment on Death or Major Disability at 14 Days or Hospital Discharge

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Antihypertensive Treatment</th>
<th>Control</th>
<th>Odds Ratio (95% CI)</th>
<th>Antihypertensive Treatment Better</th>
<th>Control Better</th>
<th>P Value for Homogeneity</th>
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<td>93总, 89 (95.7%)</td>
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<td>&lt;3</td>
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<td>Thrombotic</td>
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<td>Embolic</td>
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<td>Lacunar</td>
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<td>Overall</td>
<td>2031总, 683 (33.6%)</td>
<td>2027总, 681 (33.6%)</td>
<td>1.00 (0.88–1.14)</td>
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Figure 4. Effect of Antihypertensive Treatment on Death or Major Disability at 3 Months

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<th>Subgroup</th>
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<td>Lacunar</td>
<td>362</td>
<td>329</td>
<td>48 (13.3)</td>
<td>54 (16.4)</td>
<td>0.78 (0.51-1.19)</td>
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<td>1987</td>
<td>500 (25.2)</td>
<td>502 (25.3)</td>
<td>0.99 (0.86-1.15)</td>
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Permissive Hypertension: Recommendations

- No thrombolytic therapy
  - Permissive hypertension up to 220/120 mmHg
  - Unless contraindications exist (e.g. MI, aortic dissection)
  - Cautious reduction of BP (e.g. 15-20% reduction in MAP or SBP in first 24 hours)
  - Choice of agent controversial; labetalol, nicardipine don’t raise ICP.

- Thrombolytic therapy
  - BP <185/110 mmHg prior to t-tPA administration
  - BP <180/105 mmHg after r-tPA, for the first 24 hours
Induced Hypertension

• Should blood pressure be raised with pressors (induced hypertension) in patients with relative hypotension?
  – Not routinely. *Class IIb; Level of Evidence B*
  – Data derive from case reports, case series, small retrospective studies, very small randomized trials.
  – No definitive conclusions regarding safety and efficacy
Orolingual Angioedema

- 1-8%; often mild and transient
- Increased risk*
  - ACEI
  - CT findings of ischemia in the frontal or insular cortices
- Up to 2 hours following IV rtPA infusion
- Treatment
  - In cases of life-threatening angioedema, laryngospasm, and hypotension, the infusion should be stopped immediately
  - Antihistamines
  - IV corticosteroids
  - Epinephrine
  - Endotracheal intubation
- E.g. 50 mg IV diphenhydramine, 50 mg IV ranitidine, and 10 mg IV Decadron
- Severe cases: 0.3 mg IM epinephrine

Symptomatic ICH

- Evidence of hemorrhage seen on CT or MRI associated with an increase in the NIHSS score of 4 or more points\(^1\)
- 6.4% of patients treated with IV rtPA.
- 2.4% of patients (3 to 4.5 hours)
- Most sICH occur within the first 24 hours following treatment

Subtypes of hemorrhagic transformation

Risk for Symptomatic ICH

- Higher stroke severity and older age
- Heart failure, ischemic heart disease, Afib, hyperglycemia, diabetes mellitus, renal impairment, hypertension in the first 24 hours, preceding antithrombotic use, thrombocytopenia, leukoaraiosis (cerebral white matter disease), and persistent arterial occlusion after IV rtPA infusion

- No significant difference in rates of sICH between those who underwent thrombectomy and patients who received standard care


Predictors of Symptomatic ICH after Mechanical Thrombectomy in AIS due to Large Vessel Occlusion [ICA or Proximal M1-MCA]

- High baseline NIHSS
- Hyperglycemia
- Prior antiplatelet therapy

Symptomatic ICH: Management

• If sICH suspected, stop tPA
• 10 units of cryoprecipitate
• Antifibrinolytics:
  – IV tranexamic acid 10 mg/kg to 15 mg/kg over 20 minutes
  – IV ε-aminocaproic acid 5 g
• Fibrinogen levels after administration; if < 150 mg/dL, additional cryoprecipitate
• Surgical intervention: Consider in select patients when the rtPA has been adequately reversed

Massive (“malignant”) Cerebral Infarction

- Medical Management
- Surgical Management
Malignant Cerebral Infarction → Cerebral Edema

• 5 to 10% of stroke patients\(^1\)
• Brain infarction resulting in life-threatening space-occupying edema
• Usually due to occlusion of the ICA or proximal MCA\(^2\)
• Time frame
  – Between 72-96 hours after stroke onset \(^3\)
  – Can occur within 24 hours
  – 68% ~48 hours
  – 88% ~72 hours

“Malignant” Infarction

- High risk for brain herniation (uncal, subfalcine)
- Nearly 80% mortality rate
- No medical therapy absolutely effective
Clinical Features

- Headache
- Nausea/Vomiting
- Declining level of consciousness
- Paralysis ipsilateral to hemispheric infarction
- Brainstem signs
- Cushing’s triad (hypertension, bradycardia, irregular respiration)
“Malignant” Infarction
Clinical Predictors

- Onset of nausea/vomiting within 24 hours of stroke onset
- SBP > 180mmHg after 12 hours from symptom onset
- History of HTN
- History of Heart failure
- Elevated white cell count
- Younger age
- Female sex
- No history of prior stroke
- Abnormal ipsilateral circle of Willis
- Carotid occlusion

- NIHSS > 15 for non-dominant
- NIHSS > 20 for dominant hemisphere

References:
Radiological Predictors

• **CT**
  - Frank hypodensity within 6 hours
  - > 1/3 of MCA territory
  - Involvement of MCA + other territories (ACA, PCA, anterior choroidal)
  - Midline shift of septum pellucidum of > 5 mm MRI

• **MRI**
  - Infarct volume: DWI/ADC volume > 80 ml within 6 hours


Medical Management

• Frequent neurological exams
  – Avoid hypercapnea
  – Normoglycemia. Goal 140-180
  – Euvolemia: Avoid HYPOTonic solutions
  – Normotension (avoid cerebral vasodilators)
  – Correct HYPONatremia
  – HYPERtonic saline, Osmotic diuretics
  – Normothermia
  – Hypothermia?
  – Barbiturates?

Osmotic Therapy

• Patients with clinical and radiographic evidence of swelling.
  ➢ Mannitol
    – Dosing: 0.5 g/kg to 1 g/kg IV every 4 to 6 hours
    – Serum osmolarity between 310 mOsm/L and 320 mOsm/L
    – Osmolar gap 15-20
    – Mannitol toxic to the renal tubular cells
    – Diuretic effects: Can cause hypotension and hypovolemia.

➢ Hypertonic saline
  – Different concentrations
  – 23.4%: 30cc = 120 meq Na. Compare with 3% 1000cc = 513 meq Na.
  – Goal serum sodium 150 mEq/L to 155 mEq/L.
  – Volume overload
Surgical Therapy
Decompressive Craniectomy

• Benefits/ goals: To reduce ongoing brain injury
  – Immediate reduction in ICP
  – Improvement in blood flow
  – Herniation of brain out (through craniectomy defect) instead of in or down
    • i.e. decompression of vital structures: brainstem
Head CTs on admission and after DHC in severe hemispheric infarction

W. Taylor Kimberly, and Kevin N. Sheth Neurology 2011;76:S50-S56
Decompressive Hemicraniectomy for malignant MCA Infarction
Prospective Randomized Clinical Trials

- DECIMAL
- DESTINY
- HAMLET
  - DESTINY II
STUDY DESIGN: 4 RCT’s

DECIMAL
- Age: 18 - 55 yrs. 38 Patients
- Size: >50% MCA territory/ DWI volume > 145 cm³
- Time: Within 6H of R/ 30H of onset
- “Favorable” mRS <=3 @6months

DESTINY
- Age: 18 - 60 yrs. 32 patients
- Size: >2/3 MCA territory + part of BG
- Time: Sx >12 and <36 H of onset
- Outcome: mRS 0-3 vs. 4-6 @ 6 months

DESTINY II
- 112 Patients
- Age: 61 and older (Md=70)
- Size: >2/3 MCA territory + part of BG
- Time: Sx <48 H of onset
- Outcome: mRS 0-4 @ 6 months

HAMLET
- Age: 18 - 60 yrs. 64 patients
- Size: >2/3 MCA territory
- Time: Sx <96 H of onset
- Outcome: mRS 0-3 vs. 4-6 @ 1 year
## MODIFIED RANKIN SCALE (MRS)

<table>
<thead>
<tr>
<th>Score</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No symptoms at all</td>
</tr>
<tr>
<td>1</td>
<td>No significant disability despite symptoms; able to carry out all usual duties and activities</td>
</tr>
<tr>
<td>2</td>
<td>Slight disability; unable to carry out all previous activities, but able to look after own affairs without assistance</td>
</tr>
<tr>
<td>3</td>
<td>Moderate disability; requiring some help, but able to walk without assistance</td>
</tr>
<tr>
<td>4</td>
<td>Moderately severe disability; unable to walk without assistance and unable to attend to own bodily needs without assistance</td>
</tr>
<tr>
<td>5</td>
<td>Severe disability; bedridden, incontinent and requiring constant nursing care and attention</td>
</tr>
<tr>
<td>6</td>
<td>Dead</td>
</tr>
</tbody>
</table>
Decompressive Hemicraniectomy

• Does DHC improve outcomes after stroke?
  – Which outcomes?

• What factors guide patient selection?
  – Age?
  – Side of stroke?

• What is the optimal timing of DHC after symptom onset?
Decompressive Hemicraniectomy
Pooled Analysis of 3 RCT

• Pre-planed (prospective) pooled analysis of the 3 European trials
• Individual data for patients aged 18-60 yo who had DHC w/in 48 hrs for large MCA infarction (either hemisphere)
• Primary Outcome: 1-year dichotomized mRS (0-4 vs. 5 or death)
• Secondary Outcomes:
  a) 1-year case fatality
  b) mRS 0-3 vs. 4-death

Pooled Analysis of DECIMAL DESTINY and HAMLET

**Figure 1:** Distributions of the scores on the mRS and death after 12 months for patients treated with or without decompressive surgery

ARR 49%
Decompressive Hemicraniectomy

- Large Supra-tentorial stroke:
  - For age < 60, 78% will survive, nearly half will be moderately-severe to severely disabled, nearly half will have depression
  - For age > 60, less benefit

- Decisions regarding DHC should be made on an individual basis
STATE Criteria for Immediate Neurosurgical consultation for Hemicraniectomy for malignant MCA infarction

- **Score:**
  - GCS ≤8
  - NIHSS ≥15 (non-dominant)
  - NIHSS ≥ 20 (dominant)

- **Time:** ≤48 hrs since onset

- **Age:** ≤60 years

- **Territory:** Infarct volume >150 cm³ or >50% MCA territory infarction

- **Expectation:** Reasonable life expectancy

If all criteria met, *urgent hemicraniectomy within 4-6 hours*

**Emergent hemicraniectomy:**

Above PLUS

- Early signs of herniation: Asymmetric pupil size
- Midline shift: >10mm at septum pellucidum or >5mm at pineal gland
Cerebellar Infarction

- Often fatal due to small posterior fossa compartment
- Edema
  - Direct compression 4th ventricle, non-communicating hydrocephalus
  - Direct compression of brainstem
  - Upward or downward cerebellar herniation
Suboccipital Craniectomy

- Less evidence - case series
- Generally agreed that SOC is lifesaving
- Little data to guide timing, patient selection
Cerebellar ischemic stroke

Mass effect?

No → Observe

Yes

- Hydrocephalus with 4th ventricle obliteration
- Neurologic deterioration referable to brainstem compression in opinion of treating physician
- Neurologic deterioration suspected due to brainstem compression that improves with osmotic therapy

Yes to ANY of above → Urgent decompressive surgery

No to ALL of above → Increasing edema on serial scans over 3-5 days post stroke onset?

Yes → Consider prophylactic decompressive surgery

No → Observe
Initial Stabilization and routine ICU issues

- Airway and ventilation
- Hemodynamic, cardiac, and fluid status
- Temperature and glucose
- Seizures
- Anemia and transfusion
- VTE prevention and treatment
- End-of-life care, organ donation
ENLS - Emergency Neurological Life Support

ENLS Airway
## Effect of General Anesthesia

### Table 4. Independent Predictors of Mortality After Endovascular Therapy for AIS

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.05 (1.04–1.07)</td>
<td>0.00001</td>
</tr>
<tr>
<td>GA</td>
<td>1.68 (1.23–2.30)</td>
<td>0.00001</td>
</tr>
<tr>
<td>TIMI 0/1 recanalization</td>
<td>1.80 (1.29–2.50)</td>
<td>0.00005</td>
</tr>
<tr>
<td>Symptomatic ICH</td>
<td>4.09 (2.49–6.72)</td>
<td>0.00001</td>
</tr>
<tr>
<td>Carotid terminus occlusion</td>
<td>1.60 (1.09–2.33)</td>
<td>0.015</td>
</tr>
<tr>
<td>NIHSS score &gt; 15</td>
<td>2.12 (1.47–3.05)</td>
<td>0.00001</td>
</tr>
</tbody>
</table>

TIMI indicates Thrombolysis In Myocardial Infarction, and ICH, intracranial hemorrhage.
Effect of Conscious Sedation vs General Anesthesia on Early Neurological Improvement Among Patients With Ischemic Stroke Undergoing Endovascular Thrombectomy: A Randomized Clinical Trial

Silvia Schönenberger, MD; Lorenz Uhlmann, MSc; Werner Hacke, MD, PhD; Simon Schieber, MD; Sibu Mundiyapuranath, MD; Jan C. Purrucker, MD; Simon Nagel, MD; Christina Klose; Johannes Pfaff, MD; Martin Bendszus, MD; Peter A. Ringleb, MD; Meinhard Kieser, PhD; Markus A. Möhlenbruch, MD; Julian Bösel, MD, FNCS

SIESTA TRIAL
Tracheotomy

• 15-35% require tracheotomy
  – Prolonged mechanical ventilation
  – Severe dysphagia
  – Bulbar palsy

• Optimal timing of tracheostomy in ventilated patients??
Stroke-Related Early Tracheostomy Versus Prolonged Orotracheal Intubation in Neurocritical Care Trial (SETPOINT) A Randomized Pilot Trial

Julian Bösel, MD; Petra Schiller, PhD; Yvonne Hook, MD; Michaela Andes, MD; Jan-Oliver Neumann, MD; Sven Poli, MD; Hemasse Amiri, MD; Silvia Schönenberger, MD; Zhongying Peng, MD; Andreas Unterberg, PhD; Werner Hacke, PhD; Thorsten Steiner, PhD

- Ischemic and hemorrhagic stroke in the Neuro ICU
- 60 Patients (20 AIS, 26 ICH, 14 SAH)
- **Feasibility and Safety**
- Early tracheotomy (day 1-3 from intubation) vs. Standard (7-14 from intubation)
- Primary outcome: ICU LOS.
- No differences in ICU LOS (Median 18d)
- Early Tracheotomy group:
  - Lesser use of sedatives (42% vs 62%; p=0.02)
  - Lower ICU mortality (3 vs 14 deaths; 10% vs 47%; p<0.01)
  - Lower 6m mortality (8 vs 18 deaths; 27% vs 60%; p=0.02)
Pulmonary and Cardiac considerations

Pulmonary

- Larger strokes often have associated:
  - Decreased levels of arousal
  - Poor airway protection
- Primary brainstem events may warrant even earlier attention to airway protection
- Ventilator must take into account the level of PEEP (may impair venous return/increase ICP)

Cardiac

- MI is common in the acute stroke setting, as are atrial and ventricular dysrhythmias
- In 50/738 ischemic stroke patients, strong correlation of MI with involvement of right insula was found\(^1\)
- A meta-analysis of 65,966 stroke and TIA patients found annual risks of \(^2\):
  - 2.1% for non-stroke vascular death
  - 2.2% for total MI
  - 0.9% for non-fatal MI
  - 1.1% for fatal MI

Glucose Control: Hyperglycemia

- Hyperglycemia is common - occurs in up to 50%
- Independently associated with poor outcomes
  - Larger stroke
  - More infections
  - Higher mortality
  - More disability
  - More post-thrombolytic ICH
  - ? less effective r-tPA

- May vary by stroke type
  - Moderate hyperglycemia may be associated with favorable outcome after lacunar stroke.*

*Brain. 2007;130:1626-1630
Glucose Control

• *Cochrane meta-analysis* (2011, n=1,296):
  – IIT (72-135 mg/dl) increased risk of symptomatic hypoglycemia but did not affect functional outcome, death, or final neurological deficits.

• *INSULININFARCT trial* (2012, Stroke):
  – IIT (< 126 mg/dl) provided superior control c/w SQ insulin
  – BUT associated w/ larger infarct size.
  – Similar SAE and mortality rates
  – Not powered to detect clinical changes.

• *SHINE trial* (ongoing):
  – Multicenter RCT
  – IIT (80-130 mg/dL) vs. < 180 mg/dl.
Blood Glucose Target

- Current AHA/ASA Recommendations:
  - Glucose goal 140-180 mg/dl, with insulin infusion if needed
Temperature Control

Fever

• Fever affects up to 50% of AIS patients
• Independently associated with poor outcome.
• Relative risk of poor outcome is 2.2 for every 1°C elevation in admission temperature \(^1\)

Goals
- Treat fever itself
- Evaluate and treat infections
- No evidence that this improves outcome.
- Antipyretic medications are largely ineffective (PAIS, PAIS II).
- Non-pharmacological means

\(^1\)Lancet 1996;347:422
Therapeutic Hypothermia: Lack of effectiveness

- Schwab et al. Stroke 1998
- Schwab et al. Stroke 2001
- Gulama et al. COOLAID trial. Acad Emerg Medic. 2006
- ICTus-L Hemmen et al. Stroke 2010. After IV tPA
- Su et al. Stroke 2015. Massive AIS
- Copenhagen Stroke Group – feasibility and efficacy
- Els et al 2006 safety and outcomes: Non significant
- Piironen et al 2014 – safety and feasibility of mild hypothermia (35) post tPA
- ICTuS 2: 2016: No differences in mortality or 90 day mRS
Hemoglobin Management
Anemia

• Anemia occurs in up to 97% of severe AIS patients in ICU
• Anemia —> decreased tissue O2 delivery.
• However, increased hemoglobin —> hyper viscosity, which may exacerbate ischemia.
• “U-shaped” relationship between hemoglobin and outcome after AIS and ICH.
Early Prophylaxis of Systemic Complications

- **DVT Prophylaxis**
  - Compressive devices: Ted hose, pneumatic compression boots
  - LMWH (or SQ UFH if renal insufficiency)
  - LMWH appears to be superior to UFH in AIS

- **Respiratory (Chest PT, positioning)**
  - Aspiration, VAP prevention
  - Atelectasis

---

Early Prophylaxis of Systemic Complications

• GI prophylaxis and motility
  – Assess and document swallowing
  – Discourage NPOx24 hrs rule as a standard
  – LHI patients with dysphagia should receive a nasogastric tube as soon as possible
  – Early feeding (when possible)
  – H1 blockers, PPIs
  – Stool softeners, bowel motility agents

• GU tract complications
  – Indwelling catheter/UTI
  – Bladder atonia
New Therapies

• IV Glyburide
• Selectively blocks sulfonylurea receptor 1 (SUR1)-transient receptor potential melastatin 4 (TRPM4) channel: that promotes cerebral edema
• Decreases water accumulation in the brain, improves survival, and facilitates neurological recovery in rodent models
Safety and efficacy of intravenous glyburide on brain swelling after large hemispheric infarction (GAMES-RP): a randomised, double-blind, placebo-controlled phase 2 trial


Lancet Neurol 2016; 15: 1160–69

<table>
<thead>
<tr>
<th></th>
<th>Intravenous glyburide (n=41)</th>
<th>Placebo (n=36)</th>
<th>p value</th>
<th>Effect size (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–4 at 90 days without decompressive craniectomy</td>
<td>17 (41%)</td>
<td>14 (39%)</td>
<td>0.77</td>
<td>OR 0.87 (0.32 to 2.32)*</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decompressive craniectomy or death by day 14</td>
<td>15 (37%)</td>
<td>16 (44%)</td>
<td>0.48</td>
<td>OR 0.72 (0.29 to 1.80)</td>
</tr>
<tr>
<td>Change in ipsilateral hemispheric swelling 72–96 h (cm³)</td>
<td>68 (36–105)</td>
<td>78 (52–133)</td>
<td>0.28</td>
<td>Mean difference -13.4 (-43.4 to 16.6)</td>
</tr>
<tr>
<td>Change in lesional swelling 72–96 h (cm³)</td>
<td>58 (35–98)</td>
<td>78 (45–121)</td>
<td>0.41</td>
<td>-6.6 (-39.8 to 26.5)</td>
</tr>
<tr>
<td>Tertiary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mRS 0–4 at 90 days†</td>
<td>25 (61%)</td>
<td>17 (47%)</td>
<td>0.23</td>
<td>OR 1.75 (0.71 to 4.32)</td>
</tr>
<tr>
<td>Decompressive craniectomy at 90 days†</td>
<td>13 (32%)</td>
<td>8 (22%)</td>
<td>0.35</td>
<td>OR 1.63 (0.58 to 4.53)</td>
</tr>
<tr>
<td>Midline shift of the brain from baseline to 72–96 h (mm)</td>
<td>4.6 (2.0–6.6)</td>
<td>8.5 (5.0–14.2)</td>
<td>0.0006</td>
<td>-4.3 (-6.3 to -2.4)</td>
</tr>
<tr>
<td>MMP-9 during study drug infusion (ng/mL) at 24–72 h†</td>
<td>211.4 (138–1)</td>
<td>345.8 (250–7)</td>
<td>0.006</td>
<td>-134.4 (-224.8 to -43.9)</td>
</tr>
<tr>
<td>All cause mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-hospital deaths</td>
<td>3 (7%)</td>
<td>5 (14%)</td>
<td>0.46</td>
<td>..</td>
</tr>
<tr>
<td>7 day</td>
<td>4 (10%)</td>
<td>5 (14%)</td>
<td>0.73</td>
<td>..</td>
</tr>
<tr>
<td>30 day</td>
<td>6 (15%)</td>
<td>13 (36%)</td>
<td>0.03</td>
<td>..</td>
</tr>
<tr>
<td>90 day</td>
<td>7 (17%)</td>
<td>13 (36%)</td>
<td>0.06</td>
<td>HR 0.49 (0.21–1.13)</td>
</tr>
<tr>
<td>Post-hoc analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in ipsilateral hemispheric swelling for patients without decompressive craniectomy (cm³)§</td>
<td>49 (25–81)</td>
<td>77 (53–105)</td>
<td>0.04</td>
<td>-29.3 (-62.3 to 3.8)</td>
</tr>
<tr>
<td>Change in lesional swelling for subset of patients without decompressive craniectomy (cm³)§</td>
<td>41 (27–69)</td>
<td>75 (37–100)</td>
<td>0.15</td>
<td>-21.1 (-56.7 to 14.5)</td>
</tr>
</tbody>
</table>

MMP-9 elevation is associated with several stroke-related complications, including brain edema after stroke