Malignant Cerebral Infarction

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Disclosures

• Dr. Streib is a member of the ICSI Stroke Guidelines Committee (no reimbursement)

• Dr. Reshi is a member of ENLS marketing committee of Neurocritical Care
Disclosures

• We have no financial relationships or other conflict of interests to disclose, and will not discuss off label use and/or investigational use in my presentation

• Research grants:
  – Dr. Reshi: Local University grant for a pilot project.

• Ownership interest in: None

• No Outside consultancy role
Outline

1. Pathophysiology of Malignant Cerebral Infarction (MCI)

2. Treatment Options & Review of Evidence:
   - Medical
   - Surgical

3. Clinical Decision Making

4. Summary
Abbreviations

- mRS = modified Rankin Scale
- NIHSS = NIH Stroke Scale
- TLSW = time last seen well
- DC = decompressive craniectomy
- Early DC = DC within 48 hours of onset
- MCI = malignant cerebral infarction
- LOC = Level of Consciousness
Malignant Cerebral Infarction

Definition: Large acute ischemic stroke, typically within the MCA territory, complicated by life-threatening cerebral edema that may lead to brain herniation, coma, respiratory arrest, and death.

Natural History of MCI: mortality rate = 80%

Definition
Mechanism of Injury

• Cerebral Edema:
  – What kind of edema is this?
    • Cytotoxic --- Majority
      – Does not respond to hypertonic solution or mannitol.
    • Vasogenic --- very small
      – Responds to hypertonic, mannitol and steroids etc.
Cytotoxic Edema
Vasogenic Edema
Progression

• 0-24 hours: No major shift
  – Necrotic core.
Progression

• 24-72 hours: Penumbra progresses to necrosis
  – Progressive edema
  – Midline shift
  – ICP elevation leading to decreased cerebral perfusion, extension of infarction
Progression

• > 72 Hours: Worsening cytotoxic edema
  – Increase in ICP
  – Midline shift leading to prolonged decrease LOC: intubation, aspiration PNA, DVT, etc
  – Lethal herniation
Who is likely to develop MCI?

- Early CT suggesting > 50% of MCA territory
- Pineal Gland displacement
- Midline shift > 5mm within first 2 days
- > 2/3rd involvement on CT perfusion maps.
- DWI lesion > 145 cubic cm.
- Multiple vascular territories
- T Occlusion of distal ICA
What we are treating?

- Ischemic infarct
- Associated Cerebral Edema
  - Cytotoxic
    - Not Treatable with Medical Therapy
- Midline shift $\rightarrow$ Decreased LOC
  - No Evidence that Medical Therapy is effective
  - Evidence to the contrary
- Increased ICP $\rightarrow$ secondary injury
  - Only thing we can treat with medical Rx.
  - A Bridge to definite therapy
  - Already too late
Examine the Evidence

• Head Elevation
  – More significant drop in ICP vs CPP (P.0001)
  – No studies with improved benefit, actually recent study showed no benefit.

• Cooling
  – Mortality in DC vs HT was 12 vs 47%
Medical Therapy

• Mannitol
  – Bereczki D, Stroke 2003;34:1730–5
    • 800 patients observational study
    • No mortality or functional benefit.
  – Cochrane report
    • Bereczki D, Cochrane Database Syst Rev 2007;(1)
    • 226 pts in three randomized trials
    • No benefit.
Medical Therapy

• Hypertonic solution
  – No RCT
  – No case reports or short series
  – Schwarz S, Stroke 2002;33:136–40
    • ICP dropped and CPP improved.
    • Mortality was 50% in this cohort.

• Glycerol
  – Righetti E, Cochrane Database Syst Rev 2004;(2)
  – No difference between Glycerol and control
Medical Therapy

• Barbiturates
  – Reduce ICP
  – Debunked in Trauma --- Cochrane
    • Successfully Rxed ICP in MCI
    • Mortality was 91%

• Corticosteroids
  – Cochrane Review Slivka AP, Exp Neurol 2001;167:66–172
  – 7 RCT’s, 453 patients. No mortality/functional benefit.
Summary of Medical Therapy

• No definitive medical treatment
• May increase mortality
• Contrary to belief
  – Increases shift
  – Does not reduce cytotoxic edema
• Thus --------
NEED FOR MEDICAL THERAPY POINTS TO A FAILURE IN EARLY RECOGNITION AND TREATMENT OF MCI
SHOULD ONLY BE USED AS A BRIDGE TO A MORE DEFINITIVE THERAPY IF ONE IS AVAILABLE!!!!!
Transition

• May I say that the medical therapy works for what it is supposed to do i.e. Reduce ICP
• We should not allow ICP to rise in MCI
  – Already too late --- secondary injury already started.
• If needed it is only a Bridge and not a definitive therapy.
Decompressive Craniectomy

1. Reversed question mark skin incision
2. Craniectomy including frontal, parietal, temporal occipital bones
3. Opening of the dura and insertion of dural patch
4. Fix dura at craniotomy margins
5. Re-approximation of temporal muscle and skin flap
6. Cranioplasty in 6-12 weeks

Figure 1. Decompressive craniotomy, A, midline; B, incision in skin.

Figure 3. Decompressive craniotomy, A, additional area of bone removal; B, area of the temporal floor at the lesser wing of the sphenoid bone.
50-year-old female enrolled in DECIMAL, randomized to medical management group. A.) Initial Head CT  B.) MRI 5hrs from presentation C.) 28hr Head CT

Vahedi K et al. Stroke. 2007;38:2506-2517
Malignant MCA Infarct treated with DC

22-year-old woman enrolled in DECIMAL
A.) Admission MRI.  B.) HCT s/p early DC  C.) 12 month MRI (mRS 3)

Vahedi K et al. Stroke. 2007;38:2506-2517
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Clinical Case

- 47 yo healthy male with PMHx of HTN
- TLSW 640PM, arrival at 940PM
- NIHSS 16, RMCA syndrome
Questions

1. Is this patient a good candidate for DC?
2. When is the optimal time to perform DC?
   A. Now
   B. Less than 48hrs
   C. When the patient develops signs of herniation
   D. Only if he progresses to coma
   E. This patient will likely not require DC
Questions

3. Does early DC increase survival?
4. Does early DC decrease morbidity?
5. What is the approximate likelihood of a “favorable outcome”, (mRS 0-3) with early DC?
   A. 0%
   B. 25%
   C. 50%
   D. 75%
AHA/ASA Guidelines

- Decompressive surgery for malignant edema of the cerebral hemisphere is effective and potentially lifesaving (*Class I; Level of Evidence B*), but......

- Advanced patient age and patient/family valuations of achievable outcome states may affect decisions regarding surgery

Jauch et al. AHA/ASA Guidelines for Management of Acute Ischemic Stroke 2013
Historical Context of DC for MCI

1901
Dr. Emil Theodor Kocher first describes DC

1990s-2000s
Advances in neuroimaging and neurocritical care make DC a realistic treatment option

Early 2000s
Clinical data suggests significant improvement in mortality with DC, long-term outcomes less devastating than expected

2007
A landmark interim pooled analysis of 3 ongoing RCTs of DC demonstrates benefit of DC in both mortality and morbidity

2009
Upon completion of the three DC RCTs, the results no longer show a benefit for favorable functional outcome

2014
DESTINY-II demonstrates decreased mortality for patients > 60 yo and improvement in “acceptable” functional outcomes

Present Day
Significant debate surrounding DC for MCI persists
DC Remains Controversial

There is a clear survival benefit, but are we increasing survival at the expense of major disability?

1. No individual RCT or pooled final analysis has shown benefit for excellent or favorable functional outcomes (mRS 0-3)
2. Continued poor understanding of clinical outcomes by many, including treating neurologists and neurosurgeons
   - Impact of age, dominant hemisphere infarction, timing
Interim Pooled Analysis: HAMLET, DESTINY, DECIMAL (n=93)

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

Interim Pooled Analysis: HAMLET, DESTINY, DECIMAL (n=93)

Figure 1: Distributions of the scores on the mRS and death after 12 months for patients treated with or without decompressive surgery.
# Modified Rankin Scale (mRS)

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<tr>
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<tbody>
<tr>
<td>0</td>
<td><strong>Excellent: Independence preserved</strong></td>
</tr>
<tr>
<td>1</td>
<td><strong>Favorable: non-independent, can ambulate</strong></td>
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<tr>
<td>2</td>
<td><strong>Acceptable: cannot ambulate, not bed bound</strong></td>
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<tr>
<td>3</td>
<td><strong>Unacceptable: Totally Dependent/Death</strong></td>
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<tr>
<td>4</td>
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<td>5</td>
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Modified Rankin Scale (mRS)

Modified Rankin Scale Utility Weights

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![Modified Rankin Scale Utility Weights](image-url)
Meta-Analysis Aims

1. Is there evidence that early DC increases independent outcomes? (mRS 0-2)
2. Is there evidence that early DC increases favorable functional outcomes? (mRS 0-3)
3. Examine the impact of older age on functional outcomes
4. Create a decision algorithm
# Meta-Analysis of 6 RCTs

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of participants</th>
<th>Age, (y)</th>
<th>DC timing, (h)</th>
<th>Baseline mRS</th>
<th>Clinical and radiographic definitions of MCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jüttler 2014&lt;sup&gt;10&lt;/sup&gt;</td>
<td>109</td>
<td>&gt;60</td>
<td>&lt;48</td>
<td>≤1</td>
<td>NIHSS &gt;14 (nondominant) or &gt;19 (dominant)</td>
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<td></td>
<td>&gt;66% infarction MCA territory</td>
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<tr>
<td>Zhao 2012&lt;sup&gt;11&lt;/sup&gt;</td>
<td>47</td>
<td>18-80</td>
<td>&lt;48</td>
<td>≤2</td>
<td>Eye and motor GCS ≤9</td>
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<td>Hofmeijer 2009&lt;sup&gt;5&lt;/sup&gt;</td>
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Abbreviations: DC = decompressive craniectomy; GCS = Glasgow Coma Scale; mRS = modified Rankin Scale; MCI = malignant cerebral infarction; MCA = middle cerebral artery; DWI = diffusion-weighted imaging; NIHSS = NIH Stroke Scale.

<sup>a</sup>Preliminary publication.

<sup>b</sup>Post hoc subgroup analysis of the original trial, which enrolled patients up to 96 hours from MCI onset.

Meta-Analysis Findings

1. Early DC increased excellent (i.e. independent) functional outcomes \((\text{mRS 0-2})\)
2. Early DC increased favorable outcomes \((\text{mRS 0-3})\)

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3. Although favorable outcomes for patients > 60 yo increased, older patients had poorer overall functional recovery.
## Number Needed to Treat with DC Patients ≤ 60 years old

<table>
<thead>
<tr>
<th>mRS 0-2</th>
<th>DC vs Control</th>
<th>Risk Reduction</th>
<th>~NNT</th>
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<tr>
<td></td>
<td>16% vs 5%</td>
<td>11%</td>
<td>9</td>
</tr>
<tr>
<td>mRS 0-3</td>
<td>43% vs 22%</td>
<td>21%</td>
<td>5</td>
</tr>
<tr>
<td>mRS 0-4</td>
<td>70% vs 27%</td>
<td>43%</td>
<td>2</td>
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<tr>
<td>Mortality</td>
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**Number Needed to Treat with DC Patients > 60 years old**

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<tr>
<td>mRS 0-3</td>
<td>8% vs 4%</td>
<td>4%</td>
<td>25</td>
</tr>
<tr>
<td>mRS 0-4</td>
<td>44% vs 14%</td>
<td>30%</td>
<td>3</td>
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<tr>
<td>Mortality</td>
<td>39% vs 76%</td>
<td>37%</td>
<td>3</td>
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</table>
Clinical Decision Algorithm

Goals of care

- Maximize survival or level of functional outcome
- Quality of life
  - Minimize survival with significant disability

Function outcomes with early DC, age \( \leq 60^a \)
- mRS 0-4 acceptable
  - 69% Good quality of life
  - 9% Poor quality of life
  - 22% Death
- mRS 0-3 acceptable
  - 43% Good quality of life
  - 35% Poor quality of life
  - 22% Death

Function outcomes with early DC, age \( > 60^a \)
- mRS 0-4 acceptable
  - 44% Good quality of life
  - 17% Poor quality of life
  - 39% Death
- mRS 0-3 acceptable
  - 8% Good quality of life
  - 53% Poor quality of life
  - 39% Death

Is the probability of poor quality of life and death acceptable?

- No: Medical treatment, consider palliative care
- Yes: Early DC

Caveats

• The decision algorithm is only intended to serve as a framework to start discussions with family
• These results reflect DC performed proactively prior to herniation and <48 hours from TLSW
• Patients eligible for RCTs had no other major medical comorbidities
• No role for selecting dominant vs. non-dominant hemisphere patients for functional outcomes

Randomized Controlled Trials “Late” DC

1. HeADDFIRST: enrolled patients < 96hrs
   - No mortality benefit
   - No morbidity benefit

2. HAMLET: enrolled patients < 99hrs
   - No morbidity benefit (mRS 0-3 or mRS 0-4)
   - Mortality benefit alone
Malignant Cerebral Infarction

Large acute ischemic stroke (MCA)

Cerebral edema and increasing mass effect within the closed cranial space

↑ ICP, ↓ CBF, ↓ tissue oxygenation

New ischemia/brain injury

Brain Herniation

Coma, Respiratory Failure, Death
53 year-old right MCA stroke

DC deferred until exam worsened on day #5

What complication of delayed DC do you see?
Meta-analysis: Is life worth living?

77% would give retrospective consent for DC, n=209
-responder/survivor bias
-reflects clinical outcome
Quality of Life: 3 years after DC

• 23 of 25 MCI survivors at 1 year were alive 3 years after DC
• QOL improved from year 1 to year 3
• 52% lived at home
• 57% had symptoms of depression
  ▪ Mean Barthel Index: 70 (moderate dependency)

Guerts et al. HAMLET at 3 years. Stroke 2013
Clinical Case

- 47 yo male with PMHx of HTN
- TLSW 640PM, PUH, arrival at 940PM
- NIHSS 16, RMCA syndrome
Clinical Case Continued

- Exam stable, awake and alert
- MRI 5 hours, infarct volume = 166.5cc, proactively taken for DC next AM

36hrs later, > 1cm midline shift  Post-DC  Post-cranioplasty 2 mths later
10 months later

• Found to have Afib – on Coumadin
• Partial seizure with generalization – Keppra
• Deficits: minimal left-sided visual field cut, numbness of left 1\textsuperscript{st}/2\textsuperscript{nd} digit, mild changes in cognition, no weakness
• Returned to work full-time as forklift driver
Questions

1. Is this patient a good candidate for DC?
2. When is the optimal time to perform DC?
   A. Before herniation--less than 48hrs
   B. When the patient develops signs of herniation
   C. Only if he progresses to coma
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Questions?

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