CLEAR III: Efficiency of IVH Removal Determines mRS

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On behalf of the CLEAR III Investigators
Presenter Disclosure Information

**Issam A. Awad, MD (Surgeon Co-chair)**
- Financial disclosure: Ongoing NIH/NINDS support through R01, R21, R44, P01 mechanisms
- Support as trial co-chair and Surgical Center Director of CLEAR III (NIH/NINDS 5U01NS062851)

**Daniel F. Hanley, MD (Physician Co-chair)**
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- Unlabeled/unapproved use disclosure: Dr. Hanley holds IND #8523 (intracerebral use of rt-PA). Johns Hopkins University holds patent for using intraventricular rt-PA.

**All other authors**
- No disclosures
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ISC 2016, Los Angeles, CA
Clot Lysis Evaluation of Accelerated Resolution (CLEAR) Phase III Trial
500 subjects; 73 enrolling sites

Inclusion Criteria
- Age 18-80
- ICH ≤ 30 mL
- IVH with 3rd or 4th ventricle obstruction
- EVD placed clinically
- ICH/IVH/Catheter tract/BP stability
- Randomize 12 to 72 hours post onset
- Historical modified Rankin Scale score ≤ 1

Exclusion Criteria
- Underlying etiology other than hypertension
- Anticoagulation required; irreversible platelet count < 100,000 or INR > 1.4
- Pregnancy
- Infratentorial hemorrhage; evidence of brain stem involvement
- Uncontrollable systemic bleeding
- Other comorbidity preventing use of thrombolytic therapy

Dosing
- CT scan
- EVD

Day 1 2 3 4 5 6 7 30 365

Triangle ▲ = Diagnostic
Triangle △ = Stability
Triangle ▲ = Daily PI Review

ISC 2016, Los Angeles, CA
Clot Lysis Evaluation of Accelerated Resolution (CLEAR) Phase III Trial

- 249 subjects randomized to receive Alteplase (rtPA) 1 mg every 8 hours for up to 12 doses in the EVD, 251 cases received Saline injections
- Adaptive randomization
  - IVH size (≤20 mL; 20-50 mL; and >50 mL)
  - Thalamic/non thalamic ICH
- Groups balanced for relevant demographics and disease severity

Significantly decreased mortality at 30 and 180 days
Improved eGOS at 180 days
Pre-specified mRS 0-3 not significantly improved in the whole CLEAR III cohort
mRS at 180 days significantly improved by Alteplase in cases with initial IVH >= 20 ml

n=216
IVH <20mL
mRS 0-3 AOR=0.62 NS

n=274
IVH >=20 mL
mRS 0-3 AOR=1.84 Adjusted effect 9.7% p=0.046
Pre-specified Hypothesis
“Per Protocol” mediation of benefit via clot removal

Does enhanced IVH evacuation improve functional outcome?

• Biologic significance
• Pragmatic question in clinical practice
• Unclear prior to CLEAR III if more vigorous IVH clearance is futile, helpful, worth the risks, and how vigorous it should be
Lessons From CLEAR IVH (Phase II)

EVD in CSF optimizes ICP control & allows thrombolytic clearance of the 3rd & 4th ventricles, but not as much the IVH cast in the opposite lateral Ventricle.

Preferred catheter position: frontal region of least involved ventricle.

- Contralateral to dominant IVH cast: 6% / day
- 3rd ventricle: 26 - 49% / day
- 4th ventricle: 1% / day

Webb et al. _Stroke_ 2012
Range of Practices in the CLEAR III Protocol

- **Catheter placement**
  - First EVD catheter placed for ICP control and thrombolysis (typically contralateral to dominant IVH)
  - **Recommend** second catheter in cases of ventricular trapping, casting, mass effect or shift

- **Dosing endpoint**
  - Dosing required until 3\textsuperscript{rd} and 4\textsuperscript{th} ventricle open
  - Additional dosing **allowed** (up to 12 doses), if EVD engages the remaining clot, to clear up to 80% of IVH
Variability in EVD Placement

CLEAR III  
$n = 500$

Multiple EVD Suggested  
$n = 158$

- Single  
  $n = 47$
  - Ipsilateral  
    $n = 8$
  - Contra  
    $n = 39$
- Dual  
  $n = 111$
  - Unilateral  
    $n = 47$
  - Alternating  
    $n = 64$
  - Alternating  
    $n = 16$
- Unilateral  
  $n = 10$

Multiple EVD Not Indicated  
$n = 342$

- Single  
  $n = 316$
  - Ipsi  
    $n = 84$
  - Contra  
    $n = 207$
  - Other  
    $n = 25$

Laterality/Dosing

- Contralateral  
  $n = 246$
- Ipsilateral  
  $n = 92$
- Dual  
  $n = 137$
Variability in Catheter Placement and Dosing Resulted in **Large Variance** in IVH Evacuation

Utilization of guidelines and study protocol achieved **>80% clot removal in only 33% of Alteplase and 10% of saline patients, respectively** (p < 0.001)
Probability of **mRS 0-3 increases** with more efficient IVH removal

AOR [95% CI] = 0.93 [0.87, 1.00] \(p=0.08\) per cc of time-average clot size (IVH < 20 cc)

AOR [95% CI] = 0.96 [0.94, 0.98] \(p<0.001\) per cc of time-average clot size (IVH ≥ 20 cc)

(Adjusted for age, GCS, ICH location, and stability ICH)
Probability of **mRS 0-3 increases** with more efficient IVH removal

AOR [95% CI] = 0.97 [0.95, 1.00] \( p=0.001 \) per cc of time-average clot size (ICH - other)

AOR [95% CI] = 0.95 [0.91, 0.99] \( p<0.001 \) per cc of time-average clot size (ICH - thalamic)

(Adjusted for age, GCS, and stability ICH)
Probability of **mRS 0-3** increases with % of IVH removal

<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>AOR (95% CI)</th>
<th>AOR (95% CI)</th>
<th>AOR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per year increase)</td>
<td>0.95</td>
<td>0.95</td>
<td>0.95</td>
</tr>
<tr>
<td>GCS (per unit increase)</td>
<td>1.23</td>
<td>1.23</td>
<td>1.23</td>
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<tr>
<td>Thalamus (yes v. other)</td>
<td>0.25</td>
<td>0.25</td>
<td>0.25</td>
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<tr>
<td>IVH 20-50 mL (v. &lt; 20 mL)</td>
<td>0.47</td>
<td>0.49</td>
<td>0.49</td>
</tr>
<tr>
<td>IVH ≥ 50 mL (v. &lt; 20 mL)</td>
<td>0.13</td>
<td>0.14</td>
<td>0.14</td>
</tr>
<tr>
<td>IVH removal &gt; 90% (v ≤ 90%)</td>
<td>2.25</td>
<td>(1.10, 4.58)*</td>
<td></td>
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<tr>
<td>IVH removal &gt; 85% (v ≤ 85%)</td>
<td>1.91</td>
<td>(1.03, 3.55)*</td>
<td></td>
</tr>
<tr>
<td>IVH removal &gt; 80% (v. ≤ 80%)</td>
<td>1.38</td>
<td>(0.82, 2.33)</td>
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</tbody>
</table>

**N** 490 490 490

**P < 0.01 *P<0.05**
Cases treated with single catheters

Alteplase achieved significantly greater IVH removal with EVD ipsilateral to dominant IVH than with contralateral EVD

\[ p = 0.004 \quad \text{p} = 0.86 \]
Cases with initial IVH >=20 mL

Alteplase achieved significantly greater IVH removal with multiple EVDs than with single EVD

Alteplase: \( \Delta \text{EOT Clot (single – dual)} = -5.8 \text{ mL (95\% CI = -11.4, -0.16 mL)} \)

\( p = 0.044 \) (\( N = 69 \) Alteplase, dual catheters recommended)
Greater number of Alteplase doses enhances IVH removal (1.82% per dose, p=0.01)

$\Delta$EOT IVH volume/ dose of Alteplase: $= -0.55$ mL (95% CI = -0.88, -0.22 mL)

p = 0.001 (N = 249)
Conclusions

- Per ITT, cases with larger initial IVH volume (\(\geq 20\) mL) achieved significant functional benefit (mRS 0-3, OR 1.84) with Alteplase as compared to placebo. One life saved and one patient benefiting with mRS0-3 for each 10 cases treated.

- Cases with greater IVH evacuation achieved significantly more frequent mRS 0-3
  - OR 1.9 with >85% IVH removal
  - OR 2.2 with >90% IVH removal

- Per protocol, more efficient IVH clearance was accomplished with multiple catheters, catheters in the clot (ipsilateral to dominant IVH) and more vigorous dosing, achieving significantly better recovery (OR > 1.9) when evacuating >85% of IVH within 4 days.
What Next?

- **EVD for thrombolysis** as well as hydrocephalus/ICP control—rules are different

- **Efficacy to effectiveness (E2E) trial** (*Selker, et al., Nature- Clin Pharm Ther 2014*) to improve the evidentiary basis of the CLEAR approach in wider practice settings

- Test generalization, **CLEAR IV aiming to remove more…**
CLEAR III mRS by IVH Size, 70% EOT IVH

Saline

Alteplase

IVH<=20ml IVH>20ml

IVH<=20ml IVH>20ml

<70% removed 70%+ removed <70% removed 70%+ removed

<70% removed 70%+ removed <70% removed 70%+ removed

percent

Saline

Alteplase

MRS=0 MRS=1 MRS=2 MRS=3 MRS=4 MRS=5 MRS=6

0 20 40 60 80 100
Alteplase: $\Delta$EOT Clot (single – dual) = -5.4 mL (95% CI = -9.1, -1.7 mL), $p = 0.005$ (N = 138)

Given Dual Indicated = Yes

Alteplase: $\Delta$EOT Clot (single – dual) = -5.8 mL (95% CI = -11.4, -0.16 mL), $p = 0.044$ (N = 69)

$\Delta$EOT per Dose of Alteplase: = -0.55 mL (95% CI = -0.88, -0.22 mL), $p = 0.001$ (N = 249)

Stability IVH > 20

$\Delta$EOT per Dose of Alteplase: = -0.84 mL (95% CI = -1.38, -0.31 mL), $p = 0.002$ (N = 249)
Implications for Clinical Practice

- Greater benefit of Alteplase in cases with larger initial IVH volume; **more IVH evacuation is likely better**

- **EVD with Alteplase is not a regular EVD**; placement in dominant IVH cast or dual EVDs (departures from prevailing neurosurgical practice) increase efficiency and benefit of treatment.

- **Disciplined application of CLEAR III protocol “rules” likely contributed to the fantastic safety record**
  - Etiology screens
  - Stability procedures
  - Catheter management and removal procedures