CLONIC Proposal
Can Levetiracetam Oppress seizures in IntraCerebral hemorrhage?

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Background

- ICH is the most fatal form of stroke
- Clinically apparent seizure activity occurs in 7-17% of all patients
- The incidence of any seizure activity (clinical and EEG) is 30-40% among those with lobar ICH.
- Many providers are using prophylactic AEDs!
Are seizures associated with worse outcome?

<table>
<thead>
<tr>
<th>Study</th>
<th>n</th>
<th>Incidence</th>
<th>Association with outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vespa et al(^3)</td>
<td>63</td>
<td>28%</td>
<td>Increased midline shift</td>
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<td></td>
<td></td>
<td></td>
<td>Worse neurologic outcome</td>
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<tr>
<td>Claassen et al(^21)</td>
<td>102</td>
<td>31%</td>
<td>Hematoma expansion</td>
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<td></td>
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<td>Worse neurologic outcome</td>
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<tr>
<td>Claassen et al(^26)</td>
<td>247</td>
<td>7%</td>
<td>Worse neurologic outcome</td>
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<tr>
<td>Szaflarski et al(^27)</td>
<td>715</td>
<td>8%</td>
<td>Increased mortality</td>
</tr>
<tr>
<td>Taylor et al(^28)</td>
<td>85</td>
<td>8%</td>
<td>Improved neurologic outcome in those receiving LEV</td>
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<tr>
<td>Naidech et al(^2)</td>
<td>98</td>
<td>7%</td>
<td>Worse outcome after phenytoin</td>
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<td></td>
<td></td>
<td></td>
<td>No change after LEV</td>
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<tr>
<td>Messe et al(^1)</td>
<td>295</td>
<td>2%</td>
<td>No association with outcome</td>
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<td></td>
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<td>Worse outcome after phenytoin</td>
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</tbody>
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Current guidelines

- American Heart Association: “the utility of prophylactic anticonvulsant medication remains uncertain”
  - “Prophylactic anticonvulsant medication should not be used (Class III)” but highlights the need for further study.

- Neurocritical Care Society: No AED prophylaxis (but maybe a short course for lobar ICH and those undergoing surgical evacuation).
How might AEDs help?

- Electrographic seizures may be neurotoxic, leading to worse outcome.
- Clinical seizure activity can prolong ICU LOS and hospital LOS
- AEDs may both reduce the risk of adverse events and iatrogenesis, and provide neuroprotection and improve outcome.
Inclusion:

- Primary ICH within 24 hours of onset
- Age > 18
- Lobar location
- No clinical seizure activity prior to randomization
- Written informed consent

Randomized controlled trial
CLONIC Schema

- Patient with ICH within 24 hours of last seen well.
- Screened/consented for CLONIC
- Randomized 1:1

**Control:** Normal saline IV q12 hours ×2 doses

**Intervention:** IV LEV 1500mg q12 hours ×2 doses

- 24 hour EEG monitoring

- 24hr AEs, 7 and 90 day followup

EEG results sent for blinded central review
Phase II/III Randomized controlled trial

- Phase II Primary endpoint: Reduction in risk of “any clinical or electrographic seizure activity”
  - Futility analysis:
    - 90day mRS to determine whether to move forward with phase III.

- Phase III Primary endpoint: Improved 90 day mRS