Division of Acute Care Surgery Clinical Practice Policies, Guidelines, and Algorithms:
Post-Traumatic Seizure Prophylaxis in Patients with Traumatic Brain Injury
Clinical Practice Guideline

Original Date: 08/2005
Supersedes: 10/2014
Last Review Date: 05/2017

Purpose: To standardize the delivery of post-traumatic seizure prophylaxis in patients with traumatic brain injury.

Recommendations:
1) Patients with traumatic brain injury should receive 7 days of post-traumatic seizure prophylaxis (levetiracetam or phenytoin). (GRADE Level of Quality – moderate; USPSTF strength of recommendation – B [intervention is recommended])

Anti-Epileptic Drugs and Doses:

Phenytoin (Dilantin®)/Fosphenytoin (Cerebyx®):
- Loading dose:
  - Fosphenytoin 15 mg/kg (rounded to nearest 50 mg)
    - Administered over 150 mg/min (e.g. 1g load given over 7 minutes)
- Maintenance dose:
  - Weight | Phenytoin | Phenytoin extended release
  - <80 kg | 100 mg PO/IV q 8 hours | 300 mg PO qHS
  - 80 – 110 kg | 150 mg PO/IV q 8 hours | 400 mg PO qHS
  - >110 kg | Consult pharmacy | Consult pharmacy
  - Total phenytoin duration (IV and PO) is 7 days post-injury
  - Enteral tube feeds impair the absorption of phenytoin capsules by up to 70%, so tube feeds should be held for 2 hours before and after administration.
  - Extended release phenytoin should not be crushed and put down an enteral feeding tube as this may affect the extended release properties.

Levetiracetam (Keppra®):
- Loading dose:
  - 1g IV once
- Maintenance dose:
  - 1g PO/IV q12 hours x 7 days post-injury
    - Levetiracetam pills can be crushed and put down enteral feeding tubes without a disruption in the delivery of tube feeds.
Background:

In 1990, Temkin reported that phenytoin reduced the rate of early post-traumatic seizures from 14.2% to 3.6%.\(^1\) Though no studies have shown the prevention of early post-traumatic seizures to be associated with improved survival or neurologic outcome, the potential benefits to preventing early post-traumatic seizures are thought to include preventing the development of chronic epilepsy, decreasing derangement in acute physiology, and preventing herniation.\(^2\)

The use of levetiracetam for post-traumatic seizure prophylaxis has been increasing, presumably due to the well described side-effect profile of phenytoin including cutaneous hypersensitivity reactions, induction of the hepatic cytochrome P450 system, and drug-drug interactions.

Relevant Literature Search:

Despite the increasing use of levetiracetam, there has been no large, prospective, randomized controlled trial comparing the effectiveness of levetiracetam to phenytoin though there have been prospective observational and small randomized clinical trials.

Below are the results of a limited search for studies comparing phenytoin and levetiracetam including: randomized clinical trials, prospective observational studies, and prospective observational studies using a historical control group. The search was limited as there are a number of systematic reviews published within the past decade, which were used to ensure no relevant study was missed. For details of the search strategy, please see Appendix A.

<table>
<thead>
<tr>
<th>Author/Year</th>
<th>Study Type</th>
<th>Patients, n</th>
<th>Inclusion Criteria</th>
<th>Exclusion Criteria</th>
<th>Dosage</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Szaflarski, 2010(^3)</td>
<td>RCT (2:1 LEV to PHE)</td>
<td>S2 (18 PHE, 34 LEV)</td>
<td>Severe TBI, SBP &gt;90 mmHg, Age ≥17 years</td>
<td>No venous access, SCI, history of TBI, hemodynamic instability, anoxic injury, liver failure</td>
<td>PHE: 20mg/kg fos-PHE load, then 5mg/kg/day divided q12 hours (levels followed) LEV: 20mg/kg IV load, then 1g IV q12 hours</td>
<td>Early Post-Traumatic Seizures PHE – 5/18 (17%) LEV – 7/34 (15%)</td>
</tr>
<tr>
<td>Inaba, 2013(^4)</td>
<td>Prospective observational</td>
<td>813 (407 PHE, 406 LEV)</td>
<td>Blunt TBI Age ≥18 years</td>
<td>Pregnancy, non-survivable TBI, prehospital AED use, seizure before enrollment</td>
<td>PHE: 20mg/kg IV load, then 5mg/kg/day divided q8 hours (levels followed) LEV: 1g IV q12 hours</td>
<td>Early Post-Traumatic Seizures PHE – 6/407 (1.5%) LEV – 6/406 (1.5%)</td>
</tr>
<tr>
<td>Jones, 2008(^5)</td>
<td>Prospective observational (LEV) compared to historical control (PHE)</td>
<td>73 (PHE 41, 32 LEV)</td>
<td>Severe TBI</td>
<td>Not stated</td>
<td>PHE: unclear LEV: 500mg IV q12 hours</td>
<td>Early Post-Traumatic Seizures PHE – 0/41 (0%) LEV – 1/32 (3%) Abnormal EEG Findings PHE – 0/32 (0%) LEV – 8/42 (19%)</td>
</tr>
</tbody>
</table>

Note: in the above study, all patients were monitored with continuous EEG for 72 hours or until awake and following commands to identify subclinical seizures.

Note: in the above two center study, the majority of PHE patients were clustered at one center (396/407) and the majority of LEV patients were clustered at the other (329/406).

Note: in the above study, EEG were performed as needed – 15/32 LEV patients underwent 19 EEGs and 12/41 PHE patients underwent 19 EEGs.
### Cost Considerations:

Multiple studies have addressed the issue of cost associated with levetiracetam.\(^6,7\) However, there has recently been a reduction in the cost of levetiracetam that has alleviated. The overall cost of multiple treatment strategies are delineated below:

<table>
<thead>
<tr>
<th>Treatment Strategy</th>
<th>Load</th>
<th>Maintenance</th>
<th>Total Treatment Cost</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1g fosphenytoin</td>
<td>phenytoin 100mg IV q8&quot; x 7 days</td>
<td>$X</td>
</tr>
<tr>
<td>2</td>
<td>1g levetiracetam</td>
<td>levetiracetam 1g IV q12 x 7 days</td>
<td>$0.95X</td>
</tr>
<tr>
<td>3</td>
<td>1g levetiracetam</td>
<td>levetiracetam 1g IV q12 x 3 days levetiracetam 1g PO tab q12 x 4 days</td>
<td>$0.77X</td>
</tr>
<tr>
<td>4</td>
<td>1g levetiracetam</td>
<td>levetiracetam 1g IV q12 x 3 days levetiracetam 1g PO suspension q12 x 4 days</td>
<td>$1.10X</td>
</tr>
<tr>
<td>5</td>
<td>1g phenytoin</td>
<td>phenytoin 100mg IV q8&quot; x 7 days</td>
<td>$0.22X</td>
</tr>
</tbody>
</table>

*Actual costs cannot be displayed. However, the costs of different regimens are provided in the form of multiples of the cost of fosphenytoin load followed by 7 days of IV phenytoin.*
Appendix A: Search Strategy

As there are a number of recent systematic reviews regarding this topic, a more limited search was performed and the multiple systematic reviews were used to ensure that no relevant article was missed. Search limitations included: English language, randomized clinical trial, and prospective observational study (with or without historical control).

<table>
<thead>
<tr>
<th>Search</th>
<th>Database</th>
<th>Search Term</th>
<th>Limits</th>
<th>Total Yield: # of Articles</th>
<th># Excluded Articles</th>
<th># Included Articles</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PubMed</td>
<td>phenytoin AND levetiracetam AND traumatic brain injury</td>
<td>Clinical Trial</td>
<td>3</td>
<td>1 (outcome long-term seizures)</td>
<td>1 Prospective observational, 1 RCT</td>
</tr>
<tr>
<td>2</td>
<td>PubMed</td>
<td>phenytoin AND levetiracetam AND traumatic brain injury</td>
<td>Randomized Controlled Trial</td>
<td>2</td>
<td>0</td>
<td>1 Prospective observational, 1 RCT (both duplicates)</td>
</tr>
<tr>
<td>3</td>
<td>PubMed</td>
<td>phenytoin AND levetiracetam AND traumatic brain injury</td>
<td>Systematic Review</td>
<td>7</td>
<td>1 (retrospective study); 1 (non-trauma)</td>
<td>6</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
<td>3</td>
<td>10</td>
</tr>
</tbody>
</table>

Excluded Multiples 2

Included Papers 7 (1 RCTs, 1 Observational, 5 SRs)

Systematic Reviews evaluated:

Review of the systematic reviews failed to identify a missed randomized clinical trial, prospective observational study, or prospective observational study using a historical control.
References