Effectiveness of perioperative antiepileptic drug prophylaxis for early and late seizures following oncologic neurosurgery: a meta-analysis

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Introduction

• Prophylactic use of postoperative antiepileptic drugs (AEDs) in seizure naïve patients is controversial

• Multiple trials and meta-analyses have evaluated AED prophylaxis for patients with brain tumors and found no benefit of prophylaxis in prevention of seizures

• These studies included both surgical and non-surgical patients as well as widely different periods of treatment and follow up

• The purpose of this meta-analysis was to evaluate impact of perioperative AED prophylaxis on short- and long-term seizure incidence among patients undergoing brain tumor surgery

• This is the first meta-analysis to focus exclusively on perioperative AED prophylaxis among patients undergoing brain tumor surgery
Disclosures

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Methods

- PUBMED/MEDLINE, EMBASE, COCHRANE Central Register of Controlled Trials, clinicaltrials.gov, and SIGLE (Grey Literature) screened for records related to perioperative AED prophylaxis for patients with brain tumors
- Studies meeting pre-specified inclusion/exclusion criteria included in meta-analysis
- Risk of bias assessed using Cochrane risk of bias tool
- Early seizures defined as seizures within first postoperative week
- Mantel-Haenszel random-effects model used to analyze pooled relative risk of early seizures and total seizures associated with perioperative AED prophylaxis versus control
- Heterogeneity evaluated using I² statistic
- Publication bias evaluated using funnel plots and Egger’s test
Results

- Four RCTs involving a total of 352 patients met criteria for inclusion in meta-analysis

- There was “low” to “unclear” risk of bias across included studies
# Results

Summary of studies meeting inclusion criteria

<table>
<thead>
<tr>
<th>Study</th>
<th>Perioperative Randomization</th>
<th>Treatment period (days) / Follow up period (days)</th>
<th>Total study population (n; operation type)</th>
<th>Seizure naïve population included (n; tumor types represented)</th>
</tr>
</thead>
<tbody>
<tr>
<td>North et al., 1983</td>
<td>Phenytoin vs placebo</td>
<td>365 / 365</td>
<td>281; supratentorial craniotomy for various indications</td>
<td>81; glioma, meningioma, metastasis, sellar tumor</td>
</tr>
<tr>
<td>Lee et al., 1989</td>
<td>Phenytoin vs placebo</td>
<td>3 / 3</td>
<td>374; supratentorial craniotomy for various indications</td>
<td>85; glioma, meningioma, metastasis</td>
</tr>
<tr>
<td>Franceschetti et al., 1990</td>
<td>Phenytoin or phenobarbital vs no treatment</td>
<td>Variable (up to &gt;365) / Variable (up to &gt;365)</td>
<td>128; supratentorial craniotomy for tumor</td>
<td>63; meningioma, malignant glial tumor, metastasis</td>
</tr>
<tr>
<td>Wu et al., 2013</td>
<td>Phenytoin vs no treatment</td>
<td>7 (then taper) / 365</td>
<td>123; supratentorial craniotomy for tumor</td>
<td>123; glioma, metastasis</td>
</tr>
</tbody>
</table>
Results

- AED prophylaxis provides statistically significant reduction in risk of early postoperative seizures compared to control (RR = 0.352, 95% CI 0.130 - 0.949, p = 0.039)

Forest plot for pooled meta-analysis of effect of AED prophylaxis on incidence of early seizures (Mantel-Haenszel random-effects model)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>AED prophylaxis Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee 1989</td>
<td>0</td>
<td>44</td>
<td>3</td>
<td>41</td>
<td>11.5%</td>
<td>0.13 [0.01, 2.51]</td>
<td>1989</td>
</tr>
<tr>
<td>Franceschetti 1990</td>
<td>3</td>
<td>41</td>
<td>4</td>
<td>22</td>
<td>50.0%</td>
<td>0.40 [0.10, 1.64]</td>
<td>1990</td>
</tr>
<tr>
<td>Wu 2013</td>
<td>2</td>
<td>62</td>
<td>5</td>
<td>61</td>
<td>38.5%</td>
<td>0.39 [0.08, 1.95]</td>
<td>2013</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>147</td>
<td>124</td>
<td>100.0%</td>
<td></td>
<td></td>
<td>0.35 [0.13, 0.95]</td>
<td></td>
</tr>
<tr>
<td>Total events</td>
<td>5</td>
<td>12</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \tau^2 = 0.00; \ \text{Chi}^2 = 0.49, \ df = 2 \ (P = 0.78); \ i^2 = 0\% \\
Test for overall effect: \( Z = 2.06 \ (P = 0.04) \)
Results

- No statistically significant effect on the total incidence of seizures

Forest plot for pooled meta-analysis of effect of AED prophylaxis on incidence of total seizures (Mantel-Haenszel random-effects model)

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>AED prophylaxis</th>
<th>Control</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>North 1983</td>
<td>9</td>
<td>42</td>
<td>1.67 [0.61, 4.56]</td>
<td>1983</td>
</tr>
<tr>
<td>Franceschetti 1990</td>
<td>6</td>
<td>41</td>
<td>0.46 [0.18, 1.20]</td>
<td>1990</td>
</tr>
<tr>
<td>Wu 2013</td>
<td>15</td>
<td>62</td>
<td>1.34 [0.67, 2.68]</td>
<td>2013</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>145</td>
<td>122</td>
<td>1.03 [0.50, 2.14]</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 30, 23
Heterogeneity: Tau² = 0.22; Chi² = 4.15, df = 2 (P = 0.13); I² = 52%
Test for overall effect: Z = 0.09 (P = 0.93)
Discussion

• This meta-analysis demonstrates for the first time that perioperative AED prophylaxis for brain tumor surgery provides a statistically significant reduction in early postoperative seizure risk

• We are unable to draw conclusions about the maximally effective duration of AED prophylaxis

• Power was insufficient to perform subgroup analysis by specific tumor location or pathology

• It was not possible to pool adverse effects data because of inconsistent reporting of side effects across included studies
Summary Points

• AED prophylaxis for brain tumor surgery provides a statistically significant reduction in early postoperative seizure risk

• A well-powered RCT may help to determine ideal duration of prophylaxis and to evaluate benefit-to-risk profile of the newer AEDs

• Given the contemporary practice of AED prophylaxis as well as the findings of this meta-analysis, the question of equipoise deserves careful consideration