Acyclovir was superior to Vidarabine in the treatment of biopsy-proven HSV encephalitis.

Clinical Problem: 35-year-old male presented to the ER with a 3-day history of fever, focal seizures, & confusion. CSF analysis, EEG & MRI were suggestive of encephalitis, later confirmed by PCR to be HSV encephalitis

Clinical Question: What is the comparative effectiveness of Vidarabine and Acyclovir in the treatment of biopsy-proven HSV encephalitis?

Search Strategy:
Keywords: Encephalitis, Herpes simplex virus, Therapy, Treatment, HSV, Acyclovir
Limits: RCT, Systematic review, Human
Sources: Pubmed, Cochrane, SumSearch
Results: Without limits 1277. No meta-analysis. With limits of RCT, Human & English, we got 7 studies including that under discussion.

Clinical Bottom Lines:
As compared to Vidarabine:
1. In Biopsy-proven HSV encephalitis, Acyclovir significantly reduced mortality. p=.041, NNT=3 (95%CI 2, 9), as well as morbidity p= .029.
2. Acyclovir increased the portion of patients with no or mild impairment. p=.02, NNT=4 (95%CI 2, 20)
3. Increased survival with acyclovir seemed to come at a cost. More Acyclovir-treated survivors had severe disability. ARI=20 (0, 40), NNH=5 (95%CI 3, 712).
4. In subgroup analysis, significant reduction in mortality with Acyclovir occurred only in patients under 30 years of age. p =0.01, RRR=87%, NNT =3.
5. Poor GCS (≤ 6) at baseline, irrespective of age was associated with poor outcomes.

The Evidence:
Single-blinded, randomized controlled trial, with unknown concealment of randomization. Involved 208 patients who underwent brain biopsy & received either vidarabine or acyclovir for 10 days for presumptive HSV encephalitis at 26 institutions from Sep 1981 to Dec 1984. Only 69 patients had biopsy-proven disease. Neurological & functional assessments were scheduled at 6, 12, and 24 months. Morbidity & mortality were measured.

Data:

<table>
<thead>
<tr>
<th>Outcome</th>
<th>ACV n=32</th>
<th>Vid n=37</th>
<th>P value</th>
<th>ARR (95% CI)</th>
<th>NNT (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>death</td>
<td>6 (19%)</td>
<td>19 (51%)</td>
<td>0.041</td>
<td>32 (11, 53)</td>
<td>3 (2, 9)</td>
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<tr>
<td>Morbidity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>At 6 months</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mild/ normal</td>
<td>12 (38%)</td>
<td>5 (13%)</td>
<td>0.02</td>
<td>25 (5, 45)</td>
<td>4 (2, 20)</td>
</tr>
<tr>
<td>moderate</td>
<td>3 (9%)</td>
<td>8 (22%)</td>
<td></td>
<td>13 (4, 30)</td>
<td>8 (3, 28)</td>
</tr>
<tr>
<td>severe/dead</td>
<td>17 (53%)</td>
<td>24 (65%)</td>
<td></td>
<td>12 (11, 35)</td>
<td>8 (3, 9)</td>
</tr>
</tbody>
</table>
Comments:
· This is a single-blinded trial of unknown concealment.
· The diagnostic test these days for HSV encephalitis is PCR of the viral DNA from the CSF
· They didn’t discuss losses to follow up, if any.
· There were some baseline imbalances. More patients under the age of 30 were in the Acyclovir recipient group.
· The study does not address the issue of empirical use of acyclovir for diffuse encephalitis of unknown origin
· The disease duration before Acyclovir administration was a significant predictor of the mortality in this group p=0.04, but not in Vidarabine recipients
· Results & conclusions in this trial were similar to 2 earlier RCTs²,³.

References:

Key Words: Infection, therapy, viral encephalitis, Herpes simplex virus, acyclovir, vidarabine

Appraiser: Ahmed Al-Amri and the UWO Evidence Based Neurology Group

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