Hyperthermia, Not Hyperoxia, Exacerbates Hypoxic-Ischemic Brain Injury in the Term-Equivalent Neonatal Rat

Matthew A. Rainaldi, MD, Susan J. Vannucci, PhD, Gillian Brennan, MD, Shyama D. Patel, PhD, and Jeffrey M. Perlman, MB ChB
Department of Pediatrics, Division of Newborn Medicine, Weill Cornell Medical College, New York, NY

Introduction

- Hypoxic-ischemic encephalopathy (HIE) occurs in 1-2 per 1,000 live term births
- HIE is one of the most commonly recognized causes of severe, long-term neurologic deficits in children
  - Developmental delay
  - Mental retardation
  - Cerebral palsy
  - Seizures and epilepsy
- Damage occurs in two phases: during the acute insult and a recovery period
- Clinical and experimental data suggest that variations in both oxygen and temperature may modulate the extent of brain injury during recovery
  1, 2, 3, 5, 7, 8

Objective

- To examine the effects of hyperoxia and hyperthermia on seizures and brain injury immediately following resuscitation of the asphyxiated newborn

Hypothesis

- Neonatal rats recovered in hyperoxia and/or hyperthermia after a hypoxic-ischemic insult will have
  - More seizures
  - Larger infarcts
- Than those recovered in a normoxic-normothermic environment

Methods: HI and Recovery

- Term equivalent (P10-P11) Wistar rat pups underwent permanent surgical ligation of the right common carotid artery
- Hypoxia (8% O2, balance N2) for 60 min
- Separated into two groups for 2 hour recovery period
  - Control (T 36.5°C; FiO2 21%)
  - Treatment
    - Hyperoxia (T 36.5°C; FiO2 95%)
    - Hyperthermia (T 38.5°C; FiO2 21%)
    - Combined hyperoxia & hyperthermia (T 38.5°C; FiO2 95%)

Methods: Injury Assessment

- Animals returned to dam and sacrificed at 72 hours
- Brains extracted and flash frozen (isopentane, T -30°C)
- Coronal cryosections (18µm) from bregma -3.80 to -4.30mm, H&E stained
- Percent infarct area of ipsilateral hemisphere calculated (ImageJ, NIH software)

Methods: Seizure Detection

- EEG head mount application 4
  - Surgically attached to skull
  - One day prior to HI insult
- Data acquisition
  - Pinnacle 8200, 3 channel video EEG/EMG system 4
  - Sirenia software package
  - Seizure definition
    - Rhythmic or repetitive tracing with an amplitude that increased to more than 3 times the baseline level and lasted at least 10 seconds
    - Clinical - associated with repetitive movements
    - Subclinical - no association with movement

Results: Brain Injury

<table>
<thead>
<tr>
<th>Recovery group</th>
<th>n</th>
<th>Average infarct area (%) ± SEM</th>
<th>Deaths during recovery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normoxia-normothermia</td>
<td>35</td>
<td>61.0 ± 2.9</td>
<td>0</td>
</tr>
<tr>
<td>Hyperoxia</td>
<td>10</td>
<td>59.4 ± 6.7</td>
<td>0</td>
</tr>
<tr>
<td>Hyperthermia</td>
<td>10</td>
<td>73.2 ± 3.1*</td>
<td>0</td>
</tr>
<tr>
<td>Hyperoxia-hyperthermia</td>
<td>17</td>
<td>72.7 ± 2.8**</td>
<td>2</td>
</tr>
</tbody>
</table>

Results: Seizure Activity

- Rats recovered in a hyperthermic or combined hyperthermic-hyperoxic environment had similar mean infarcts that were larger than those recovered in normoxia-normothermia (P = 0.02)
- Rats recovered in a hyperoxic environment showed no difference in infarct versus the normothermic-normoxic recovered rats
- Two rats in the combined group died during the recovery period

• Rats recovered in a hyperthermic or combined hyperthermic-hyperoxic environment had similar mean infarcts that were larger than those recovered in normoxia-normothermia (P = 0.02)

Results: Seizure Activity

- Seizures were present in all groups during recovery
- Two rats had status epilepticus in the combined group

Summary

- Elevated temperature following HI resulted in a significant increase in infarct
- Brain injury did not appear to be exacerbated by increased oxygen concentration
- Seizures were apparent within all recovery groups post-HI
- Death and status epilepticus were seen with recovery in combined hyperoxia-hyperthermia

Conclusions

- Following HI, both clinical and subclinical seizures are likely, and may be exacerbated by increased oxygen and temperature
- Hyperthermia should be avoided during the post-resuscitation care of asphyxiated newborns
- The use of oxygen during this period requires further study

References