Intraventricular Hemorrhage in Preterm Infants: Impact on Treatment Strategies

Rajan Wadhawan, MD, MMM, CPE, FAAP
Chief of Neonatology
Walt Disney Pavilion, Florida Hospital for Children
Orlando, FL

The speaker has signed a disclosure form and indicated he has no significant financial interest or relationship with the companies or the manufacturer(s) of any commercial product and/or service that will be discussed as part of this presentation.

Session Summary

The prevalence and pathogenesis of Intraventricular hemorrhage in preterm infants will be discussed. The impact of Intraventricular hemorrhage on outcomes of preterm infants will be reviewed, as well as current and investigational therapies for prevention of Intraventricular hemorrhage.

Session Objectives

Upon completion of this presentation, the participant will:

- understand the prevalence and pathogenesis of intraventricular hemorrhage in preterm infants;
- understand the impact of intraventricular hemorrhage on outcomes of preterm infants;
- understand the current and investigational therapies for prevention of intraventricular hemorrhage.

References

References for this session can be found throughout the speaker's powerpoint presentation. A complete reference list can be obtained on request.

Session Outline

See presentation handout on the following pages.
Intra-ventricular hemorrhage: impact of treatment strategies

Rajan Wadhawan, MD, MMM, FAAP
Chief of Neonatology/Chief Medical Officer, Florida Hospital for Children
Associate Professor in Pediatrics, University of Central Florida School of Medicine

Grades of IVH

- Grade 1: Germinal matrix hemorrhage
- Grade 2: IVH without ventricular dilatation
- Grade 3: IVH with ventricular dilatation
- Grade 4: GM hemorrhage or IVH with parenchymal involvement

Papile classification: Originally developed for CT but then has been applied to cranial ultrasound as well

Pharmacological IVH prevention

- Antenatal steroids
- Indomethacin
- Newer agents

Table 5: Moderate- Severe Neurosensory Impairment in Isolated Grade I-II IVH Group in Comparison With No IVH Group After Exclusion of Other Ultrasound Abnormalities

<table>
<thead>
<tr>
<th>Gestation (wk)</th>
<th>No IVH</th>
<th>Isolated I-II IVH</th>
<th>Adjusted OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-26</td>
<td>1.18</td>
<td>0.39</td>
<td>0.77 (0.27-2.25)</td>
</tr>
<tr>
<td>27-28</td>
<td>0.65</td>
<td>0.28</td>
<td>0.24 (0.19-0.30)</td>
</tr>
<tr>
<td>30-31</td>
<td>0.35</td>
<td>0.13</td>
<td>0.20 (0.15-0.28)</td>
</tr>
</tbody>
</table>

Isolated grade I-II IVH had a 1.7 fold increased risk of moderate to severe neurosensory impairment even in the absence of PVL

Adverse Neurodevelopmental Outcomes Among Extremely Low Birth Weight Infants With a Normal Head Ultrasound: Prevalence and Antecedents

Akhil K. Lopstein, MD, P.  J. Michael L. Neo, MD, B.  Smith, MD, B.  P.  Neo, MD, and the NICHD Neonatal Network

Conclusions. Nearly 30% of ELBW infants with a normal HUS had either CP or a low MDI. Risk factors that
Antenatal steroids prior to preterm birth: Effect on IVH

<table>
<thead>
<tr>
<th>Table 1. Characteristics of the Study Population</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Age at birth (days)</td>
</tr>
<tr>
<td>Birth weight (g)</td>
</tr>
<tr>
<td>Small for gestational age</td>
</tr>
<tr>
<td>Male gender</td>
</tr>
<tr>
<td>White</td>
</tr>
</tbody>
</table>
| * Described text 
  * ECHO: serial ultrasonogram
  * Values are expressed as mean ± SD

Table 2. Parental Variables

<table>
<thead>
<tr>
<th>Table 2. Parental Variables</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td>Parental history of prematurity</td>
</tr>
<tr>
<td>Parental history of prematurity</td>
</tr>
<tr>
<td>Parental history of prematurity</td>
</tr>
<tr>
<td>Parental history of prematurity</td>
</tr>
<tr>
<td>Parental history of prematurity</td>
</tr>
</tbody>
</table>

* Two-tailed test
  * Values are expressed as mean ± SD

The New England Journal of Medicine

LONG-TERM EFFECTS OF ENDOUREDINEPHYLAL DIPHYSALIN IN EXTREMELY LOW-BIRTH-WEIGHT INFANTS

Edward E. Schimdt, M.D., Louis P. Seidler, M.D., Gene activations, M.D., Andrew Kupfer, M.D., Mark E. Vapni, M.D., and Louis L. Wright, M.D., "The Trial of Parenteral Phenylalanine in Premature Infants"
Meta analysis of prophylactic indomethacin trials

**Table 3: Results of the trials**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n of males</th>
<th>Indomethacin</th>
<th>Control</th>
<th>Risk difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head at least follow up</td>
<td>10</td>
<td>28/12 (0.71)</td>
<td>44/15 (0.77)</td>
<td>-0.06</td>
<td>3.5</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>14</td>
<td>54/13 (0.80)</td>
<td>73/13 (0.55)</td>
<td>-0.25</td>
<td>2.1</td>
</tr>
<tr>
<td>Head at delivery</td>
<td>10</td>
<td>27/10 (0.70)</td>
<td>41/15 (0.67)</td>
<td>-0.03</td>
<td>3.9</td>
</tr>
<tr>
<td>Hyperbiotic</td>
<td>14</td>
<td>54/13 (0.80)</td>
<td>73/13 (0.55)</td>
<td>-0.25</td>
<td>2.1</td>
</tr>
<tr>
<td>Head at delivery</td>
<td>10</td>
<td>27/10 (0.70)</td>
<td>41/15 (0.67)</td>
<td>-0.03</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**Table 4: Long Term and Growth Trend Discriminant Over the Years in the NNR and Other Centers**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n of males</th>
<th>Indomethacin</th>
<th>Control</th>
<th>Risk difference</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head at least follow up</td>
<td>10</td>
<td>28/12 (0.71)</td>
<td>44/15 (0.77)</td>
<td>-0.06</td>
<td>3.5</td>
</tr>
<tr>
<td>Vasoconstriction</td>
<td>14</td>
<td>54/13 (0.80)</td>
<td>73/13 (0.55)</td>
<td>-0.25</td>
<td>2.1</td>
</tr>
<tr>
<td>Head at delivery</td>
<td>10</td>
<td>27/10 (0.70)</td>
<td>41/15 (0.67)</td>
<td>-0.03</td>
<td>3.9</td>
</tr>
<tr>
<td>Hyperbiotic</td>
<td>14</td>
<td>54/13 (0.80)</td>
<td>73/13 (0.55)</td>
<td>-0.25</td>
<td>2.1</td>
</tr>
<tr>
<td>Head at delivery</td>
<td>10</td>
<td>27/10 (0.70)</td>
<td>41/15 (0.67)</td>
<td>-0.03</td>
<td>3.9</td>
</tr>
</tbody>
</table>

**Meta analysis of prophylactic indomethacin trials**

A7b: INTRACRANIAL HEMORRHAGE IN PRETERM INFANTS
Human Trials - Neonates

- Swiss Phase III study progress
  - 398 subjects enrolled
  - No safety issues
  - 36 week PMA MRI shows improved white matter and DTI
  - Follow up neurodevelopmental assessments ongoing

Erythropoietin reduces MRI biomarkers of encephalopathy of prematurity: In Press, JAMA

Phase I Trial of Neonatal Epo in Perinatal HIE (NEAT Trial)

Methods: Epo dose-escalation open-label study, N=24
All subjects met criteria for moderate HIE and were cooled
- 250 (N=3),
- 500 (N=6),
- 1000 (N=7),
- 2500 U/kg/dose (N=8)

Infants received up to 6 doses of Epo IV QOD starting at <24h of age
There were no safety issues identified

Wu et al. Pediatrics 2012;130:683-91

Spontaneous intestinal perforation in extremely low birth weight infants: association with indomethacin therapy and effects on neurodevelopmental outcomes at 18–22 months corrected age

Rajan Wadhawan, William Oh, Betty R Vohr, Stumpe Saha, Abhir Das, Edward F Bell, Abbott Liporocik, Seetha Shankaran, Barbara J Stoll, Michele C Walsh, Rose Higgins


What's New in Epo Neuroprotection?

Figure 1. Logistic regression analysis: adjusted OR for SIP versus no SIP. Early onset seizures (<0.05); sepsis at birth (<0.05); and center were also included in the logistic regression model.

Mohamed & Aly 2014

Figure 1 Spontaneous intestinal perforation in extremely low birth weight infants: association with indomethacin therapy and effects on neurodevelopmental outcomes at 18–22 months corrected age.
NEAT 1 Follow Up

- 24 infants were followed for 22 +/- 7.4 months.
- There were no deaths (6 expected)
- 1 child (4.5%) had a moderate to severe disability; this child had quadriplegic CP and GMFCS 3 (6 expected)
- MRI findings:
  - 11 (50%) had a normal brain MRI had a normal outcome

DANCE Trial (Darbepoetin Administration in Newborns undergoing Cooling for Encephalopathy. Safety and pharmacokinetics)

- 30 subjects
  - Placebo
  - 2 microgram/kg x 2
  - 10 microgram/kg x 2
- Results: No safety issues, pharmacokinetic profiles developed

Cognitive Outcomes of Preterm Infants

Randomized to Darbe, Epo, or Placebo

- Prospective, randomized, masked, multicenter study
- 500 to 1250 gm
- Study drug administered: 48 hours to 35 weeks PMA
  - N=27 Darbe (10 microgram/kg, 1 x week S.C.)
  - N=29 Epo (400 U/kg, 3 xweek subcutaneously)
  - N=24 Placebo (sham dosing 3x /week) given
- Follow up: 18 to 22 months PMA
  - Bayley Scales of Infant Development III
  - Standardized neuro exam

Bayley Scales of Infant Development and Neurodevelopmental Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Darbe N=27</th>
<th>Epo N=29</th>
<th>ESA N=56</th>
<th>Placebo N=24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Composite cognitive score</td>
<td>96.2 ± 7.3</td>
<td>97.9 ± 14.3</td>
<td>96.5 ± 11.2</td>
<td>88.7 ± 13.5</td>
</tr>
<tr>
<td>NDI (11.1%)</td>
<td>3</td>
<td>4 (13.8%)</td>
<td>7 (12.5%)</td>
<td>10 (41.7%)</td>
</tr>
<tr>
<td>NDI or Death (11.1%)</td>
<td>3</td>
<td>5 (16.7%)</td>
<td>9 (15.5%)</td>
<td>13 (48.2%)</td>
</tr>
<tr>
<td>Cerebral Palsy</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>5 (20.8%)</td>
</tr>
</tbody>
</table>

Ongoing Trials

Preterm Neuroprotection

- Swiss Trial –enrollment completed
- PENUT trial 239 / 940 enrolled!

Planned or Ongoing studies of Epo for term infants

- H Liley, Australia: PAEAN study (phase III funded)
  - N= 300, Epo 1000 U/kg; protocol matches NEAT
- J Patkai, France (phase III, enrolling)
  - N = 330, Epo 1000U/kg + HT
- A Pappas/S Shankaran: NICHD NRN
  - Phase II/III Epo + HT (proposed study– details unclear)
- Wu et al: NEAT II submission phase
**Hypothesis**: Epo treatment of babies 24 to 27 completed weeks of gestation will:

- Decrease the combined outcome of death or severe NDI from 40% to 30%, and
- Decrease death, severe and moderate NDI from 60% to 40% measured at 24-26 months corrected age.

**Secondary Hypotheses**

Neonatal Epo treatment will:

1) Be safe
2) Decrease inflammation and brain injury
3) Be associated with improved brain structure at 36 weeks postmenstrual age (MRI)

**Conclusions**

- ICH is a major morbidity affecting long term outcomes of extreme preterm infants
- Indomethacin is effective and safe in decreasing severe IVH rates but has not been shown to improve long term outcomes in these infants
- Newer agents like Erythropoeitin and Darbepoeitin appear promising and are currently under investigation for improving long term neurodevelopmental outcomes of extreme preterm infants