IVH Prophylaxis and Perinatal Neuroprotection: What Does the Evidence Show?

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

Session Summary

This session will discuss the current evidence regarding pharmacological and other strategies for preventing intraventricular hemorrhage in the premature newborn. Discussion will also include the latest evidence regarding prenatal interventions for preventing long-term neurological sequelae such as cerebral palsy.

Session Objectives

Upon completion of this presentation, the participant will be able to:

- discuss the epidemiology of premature birth in the United States and associated morbidity;
- recognize risk factors leading to long term neuro-developmental complications in premature infants;
- discuss the pathophysiology of Intraventricular hemorrhage (IVH) in the premature neonate;
- discuss the pathophysiology of periventricular leukomalacia (PVL);
- identify the clinical sequelae of IVH and PVL;
- describe evidence based approach to preventing neurologic morbidity in the preterm neonate.

References


Session Outline

See handout on the following pages.
IVH Prophylaxis and Perinatal Protection

What does the evidence show?

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Objectives

- Discuss epidemiology of premature birth in the United States and associated morbidity
- Recognize risk factors leading to long term neuro-developmental complications in premature infants
- Discuss the pathophysiology of Intraventricular Hemorrhage (IVH) in the premature neonate
- Discuss the pathophysiology of Periventricular Leukomalacia (PVL)
- Identify the clinical sequelae of IVH and PVL
- Describe evidence based approach to preventing neurologic morbidity in the preterm neonate

Disclosures

I have no potential conflicts of interest

Preterm Birth

Outcome of Extremely Preterm Infants. (From Avery’s Diseases of the Newborn, 8th Ed.)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>401-700g</th>
<th>22 – 25 wks</th>
<th>23 – 27 wks</th>
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<tr>
<td>Bilateral Blindness</td>
<td>4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Bayley II MDI Score &lt;70</td>
<td>42</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>CP</td>
<td>18</td>
<td>18</td>
<td>11</td>
</tr>
<tr>
<td>Major Impairment</td>
<td>53</td>
<td>23-49</td>
<td>20</td>
</tr>
</tbody>
</table>

Preterm Birth

- NICHD Neurodevelopmental Outcome Data for 1,151 ELBW Survivors (401 – 1000g at birth) at 18 months corrected
  - 49% had 1 or more neurodevelopmental or neurosensory deficit
    - Bayley MDI Score <70
    - Blindness
    - Deafness
    - CP

- Risk factors identified:
  - Lower birth weight
  - BPD
  - Severe IVH
  - PVL
  - Postnatal glucocorticoid exposure
  - NEC
  - Male gender

Preterm Birth

Percentage of preterm births. In 2009, there were 502,306 preterm births in the United States, representing 12.2% of live births. (From March of Dimes)
IVH

- IVH is the most common form of intracranial hemorrhage in the newborn
- Main risk factor is prematurity
- Incidence of 25% in infants 500 – 1500g
- Bleeding originates from subependymal germinal matrix
- Germinal matrix produces new brain cells that migrate outward
  - At 23 – 32 weeks the GM produces glial cells which lay down myelin
  - Production requires increased energy supply and therefore blood flow
  - Because these capillaries are not needed long term they lack support structures found in other blood vessels

- Highest risk period for IVH is first 3 postnatal days
  - Preterm infants have decreased ability to autoregulate cerebral blood flow
  - Unstable blood pressure and CBF coupled with friable capillaries yields susceptibility to IVH
  - Up to 90% of IVH appears by 72 hours

- Other risk factors
  - Male sex
  - RDS
  - Pneumothorax

Diagnosis

- Clinical Signs
  - Impaired visual tracking
  - Tight popliteal angle
  - Rolling eye movements
  - Severe IVH can present with seizures, apnea, full fontanel, anemia
  - Overall clinical correlation lacks in up to 50%

- Grading by head ultrasound (2 systems Volpe and Papile)
  - Grade I: germinal matrix only
  - Grade II: involving 10 to 50% of ventricle; no ventricular dilation
  - Grade III: involving >50% of ventricle; with ventricular dilation
  - Grade IV: extension into the parenchyma

Complications

- Post hemorrhagic hydrocephalus
  - Occurs in 25% of infants with IVH
  - Grade I and II = 7%
  - Grade III and IV = 75%
  - Increased mortality and worse developmental outcome
  - More commonly communicating hydrocephalus
  - 30% require shunting

- Periventricular hemorrhagic infarction
  - Infarction caused by venous obstruction after GMH
  - Most commonly frontal and parietal involvement
  - Usually presents as spastic hemiparesis with intellectual defects

PVL

- Greatest risk period is <32 weeks gestation
- Incidence ranges from 5 to 15% by HUS in VLBW
- Incidence slightly higher by MRI
- Can be caused by ischemia or infarction

- Periventricular leukomalacia
  - Major form of white matter injury in preterm newborns
  - Periventricular focal necrosis and diffuse gliotic white matter injury
  - Associated development of intellectual impairment and visual problems
  - Most common cause of CP

- Cerebral Palsy
  - Group of movement and posture disorders
  - Most common cause of severe motor disability in childhood
  - Prevalence of 2 per 1000 live births
  - Risk is 80 times higher in infants 23 – 27 weeks compared to term
PVL

- Factors contributing to increased risk in preterm
  - Vascular
    - Incomplete development of vessels perfusing boundary zone around ventricles
  - Circulatory
    - Impaired cerebral autoregulation
    - Anoxia, hypoxemia, hypocarbia, hypotension
  - Cellular
    - Increased glutamate levels following ischemic injury promoting neuronal cell death
    - Infection
      - Chorioamnionitis associated with higher risk of cystic PVL and CP

Prevention

- Prevent Preterm Birth!
- Delivery at specialized center
  - Rate of IVH almost double with post-natal transport
- Appropriate Resuscitation
  - Avoid hyperventilation
  - Avoid hypoxia
  - Maintain adequate MAP
  - Avoid excessive CBF
  - Correct coagulation abnormalities

Prevention//Corticosteroids

  - Pooled data of 21 studies involving 4,269 infants
  - Antenatal CS vs Placebo
    - Overall reduction of IVH and Severe IVH
    - Less childhood neurodevelopmental delay and possibly less CP
    - No benefit if first dose given following ROM > 24 hrs
    - No benefit proven in multiple pregnancies
    - No additional benefit to multiple courses
    - Greatest benefit seen when first dose given between 26 and 30 wks GA
    - Greater reduction in cystic PVL with Betamethasone compared to Dexamethasone

Prevention//Antenatal Mag Sulfate

- Simhan HN. Neuroprotective effects of in utero exposure to magnesium sulfate. UpToDate, 2012.
  - Magnesium appears to have neuroprotective effect
    - Antioxidant effects
    - Reduction in proinflammatory cytokines
    - Blockage of glutamate activated Calcium channels
    - Increased CBF
    - Prevention of large blood pressure fluctuations
Prevention//Antenatal Mag Sulfate

- Australasian Collaborative Trial of Mag Sulfate (ACTOMgSO4)
  - 1062 women < 30 weeks expected to deliver within 24 hrs
  - Mag bolus plus infusion vs. Placebo
  - Mag group had lower mortality, CP but diff not statistically significant
  - Mag group had significantly lower rates of substantial gross motor dysfunction

- Beneficial Effects of Antenatal Magnesium Sulfate (BEAM)
  - NINDS / NICHD Study
  - Multicenter placebo-controlled trial
  - 2241 women 24 – 31 weeks gestation, imminent delivery
  - MgSO4 bolus and infusion vs Placebo
  - Rate of moderate to severe CP significantly lower in Mag group
  - Benefit applied only to infants of pregnancies randomized <28 wks

- PREMAG Trial
  - 573 women < 33 wks expected to deliver within 24 hrs
  - Mag load only (no infusion) vs Placebo
  - Primary outcome of white matter injury on neonatal HUS
  - Strong trend towards protective effect of Mag against CP or Death

- Cochrane Meta-analysis
  - 5 Trials including 6145 infants
  - 4 trials demonstrated significant reduction in combined outcome of death or CP
  - Significant reduction in risk of any CP and of mod/sev CP
  - ARR of 1.7%
  - NNT to prevent one case of CP = 63

ACOG Committee Opinion #455, March 2010: Magnesium Sulfate Before Anticipated Preterm Birth

"... available evidence suggests that magnesium sulfate given before anticipated early preterm birth reduces the risk of cerebral palsy in surviving infants. Physicians electing to use magnesium for fetal neuroprotection should develop specific guidelines regarding inclusion criteria, treatment regimens, concurrent tocolysis, and monitoring in accordance with one of the larger trials."

Prevention//Delayed Cord Clamp

- Rabe H et al. Effect of timing of umbilical cord clamping and other strategies to influence placental transfusion at preterm birth on maternal and infant outcomes. Cochrane Database of Systematic Reviews 2012
  - Maximum delay 180 seconds (most 30 to 120 sec)
  - 10 trials demonstrated reduction of all grades of IVH in delayed group (no clear benefit when looking at severe IVH alone)
  - Fewer transfusions and reduced risk of NEC
  - No effect on PVL (2 trials reported) or death
  - One study reported no difference in mean Bayley II scores at 7 months of age
  - Higher peak Bilirubin in delayed clamping group

Prevention//Indomethacin

  - IV Indomethacin given within 24 hrs of birth in preterm neonates
  - Outcome measures: Death, IVH, PDA, long term ND outcome
  - 19 trials including 2872 infants met criteria
  - BWt 500 – 1750g. Three doses starting <24hrs
  - No difference in mortality
  - Treatment significantly reduced all grades of IVH
  - Rates of PDA and ligation significantly lower in Rx group
  - No effect on long term ND outcome

Prevention//Ibuprofen

- Three RCT trials published between 2004 and 2005
  - Prophylactic indomethacin vs placebo to prevent IVH
  - Trend towards decreased rates of severe IVH
  - No effect on mortality
  - Higher frequency of serious adverse events in treatment group
  - Hypovolemia
  - NEC
  - Intestinal perforation
  - Oliguria
  - PHNTN
  - One trial halted due to 3 cases of severe PHTN in treatment group
### Prevention//Ibuprofen

- Dani C et al. Prophylactic Ibuprofen for the Prevention of IVH Among Preterm Infants: A Multicenter, Randomized Study
  - 155 infants < 28 wks gestation
  - Ibuprofen or placebo within 6 hours of life
  - Trend towards slightly higher Grade II-IV IVH in treatment group
  - Rates of all IVH no different between groups
  - No difference in rates of PVL.

### Prevention//Phenobarbital

- Whitelaw A, Postnatal phenobarbital for the prevention of IVH in Preterm Infants, Cochrane Review 2008
  - Why Phenobarb?
    - Dampens blood pressure fluctuations
    - Protection against hypoxic-ischemic damage
  - Cochrane review included 10 trials with 740 infants
  - Infants <34 wks, <1500 g
  - 9 trials included loading dose, 1 didn't
  - No difference in IVH, severe IVH, post-hemorrhagic ventricular dilation, severe NDI or death
  - Increased need for mechanical ventilation in treatment group

### Conclusions

- Interventions with proven benefit:
  - Maternal transfer to perinatal center with experience in high risk delivery
  - Administration of antenatal betamethasone
  - Administration of magnesium sulfate to mothers 24 to 32 weeks gestation expected to deliver within 24 hrs
  - Develop protocol for delayed cord clamping in at risk infants.