Treatment of PPHN in Premature Infants

Inhaled Nitric Oxide Therapy in Neonates
26th March 2015, Liverpool

Disclosure

- Speaker fee for presentations

Children’s Hospital
University of Ulm, Germany

- Division of of Neonatology
  - 18 bed ICU
  - 24 bed Intermediate Care – CPAP
  - 6 bed special care unit with F/T Rooming of the mother
  - VLBWI: n=120/year, ELBWII: n=40/year

Pulmonary Hypertension in Neonates
Mortality and Morbidity

- Mortality
  - Depending on underlying disease
    - GBS-Sepsis: up to 50%
    - Median (Min-Max): 11(4-33)%
- Morbidity
  - BPD
  - Neurologic damage secondary to hypoxemia

Walsh-Byrne et al. Pediatrics 2006;118:14
Generally Accepted Principles for Treatment of PPHN

- Maintain physiology until PVR drops and/or underlying disease(s) improve
- Correct severe metabolic acidosis - do not alkalize
  - By hyperventilation – associated with BPD
  - By giving excessive Na-Bicarbonate – associated with increased organ damage
  - Both are associated with brain damage and hearing deficit
- Maintain blood pressure to limit R-L-Shunting

Targets for Current or Emerging Therapies in Pulmonary Arterial Hypertension

Treatments Described for Neonates with PPHN

- Inhaled Nitric Oxide (iNO)
- Prostacyclin
  - Intravenously
  - via Aerosol
- Sildenafil
- Milrinone
- Bosentan
- Magnesiumsulfate

Proposed Effects of Nitric Oxide on the Respiratory System

Smooth Muscle Cell

iNO is the Treatment of Choice in Full-term Neonates with PPHN

- Rationale: pulmonary vasodilatation
- Reduces the need for ECMO
  - 12 RCT’s: RR 0.65 (0.55-0.76) (www.nichd.nih.gov/cochraneononatal/Finer/Finer.html)
iNO for Treatment of PPHN in Term Newborns

Death or ECMO

<table>
<thead>
<tr>
<th>Study</th>
<th>iNO vs Control</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulm</td>
<td>7/17 (0.39)</td>
<td>1.9</td>
<td>(0.55-6.76)</td>
</tr>
</tbody>
</table>

Change in PO$_2$ after 30-60 min

<table>
<thead>
<tr>
<th>Study</th>
<th>iNO vs Control</th>
<th>PO$_2$</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ulm</td>
<td>7/17 (0.39)</td>
<td>45</td>
<td>(35,56)</td>
</tr>
</tbody>
</table>

RCT of Early vs. Delayed Use of iNO in Newborns with PPHN

- Term infants (n=56) with moderate respiratory failure (OI 10-30) less than 48h of age were randomized to
  - iNO 20 ppm
  - Control group (rescue with iNO if OI >40)
- Results:
  - 7/28 (25%) vs. 17/28 (61%) [iNO vs. Control-patients] developed an OI>40.
  - OI decreased and was significantly lower in iNO vs. Controls
  - Deaths: 1 (early iNO) vs. 2 patients (Control)
- Conclusion: Early use of iNO in term infants with moderate respiratory failure improves oxygenation and decreases the probability of severe respiratory failure

PPHN ist not Limited to Full-term Neonates

- FG 24+2 wks, 740 g
- Intubation, mech. Ventilation, Surfactant 2x
- SpO$_2$ slowly ↓ to 37 % (PaO$_2$: 18 mmHg)

Use of iNO

<table>
<thead>
<tr>
<th>Year</th>
<th>Preterm</th>
<th>Full-term</th>
</tr>
</thead>
<tbody>
<tr>
<td>2005</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2006</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2007</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2008</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2009</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2010</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2011</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2012</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2013</td>
<td>0.3</td>
<td>0.6</td>
</tr>
<tr>
<td>2014</td>
<td>0.3</td>
<td>0.6</td>
</tr>
</tbody>
</table>

- There was a 6-fold increase (0.3 to 1.8%) in the use of iNO in infants <34 wks GA between 2000 and 2008. Largest increase occurred among infants with 23-26 wks GA (0.8 to 6.6%) (Clark et al. J Perinatol 2010;30:800)
iNO in Preterm Infants for PPHN
What’s the evidence?

- 1990’s: Case-reports and cohort studies (Rescue):
  - Oxygenation ↑
  - “High” mortality and/or
  - “High” rate of IVH (IVH Grade %)
  - However: selected patient population (high risk for complications)

- 30% of all newborns with PPHN do not respond to iNO (Travadi et al. J Pediatr Pulmonol 2003:36:529)

Cochrane Review: iNO for Respiratory Failure in Preterm Infants

- Study entry <3d based on oxygenation
  - RR (95% CI) 0.90 (0.74; 1.11)
- Study entry >3d based on BPD risk
  - RR (95% CI) 1.04 (0.90; 1.20)
- Studies on routine use in intubated infants
  - RR (95% CI) 0.91 (0.74; 1.11)

Cochrane Review: iNO for Respiratory Failure in Preterm Infants

- BPD @ 36 wks PMA
  - Study entry <3d based on oxygenation
    - RR (95% CI) 0.89 (0.76; 1.02)
  - Study entry >3d based on BPD risk
    - RR (95% CI) 0.94 (0.84; 1.05)
- Studies on routine use in intubated infants
  - RR (95% CI) 0.94 (0.87; 1.01)

Cochrane Review: iNO for Respiratory Failure in Preterm Infants

- IVH Grade 3/4
  - Study entry <3d based on oxygenation
    - RR (95% CI) 0.89 (0.76; 1.02)
  - Study entry >3d based on BPD risk
    - RR (95% CI) 1.00 (0.86; 1.15)
- Studies on routine use in intubated infants
  - RR (95% CI) 0.94 (0.84; 1.05)

Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure

- NICHD network, 420 VLBWI, <34 wks GA, OI >10 after surfactant Tx
- RCT: iNO: 5 ppm vs. placebo, 10 ppm if response “incomplete” (ΔPaO₂ >20 mmHg), weaning acc. to protocol, duration max. 14d
- Prim Outcome: death or BPD (O₂ @36 wks GA)
- Trial closed after the second interim analysis (2/3 recruitment)
  - Incidence of IVH Grade 3/4 or PVL was significantly higher in the iNO group (39% vs. 27%, p=0.02)
  - 420/440 infants were recruited at this time

Studies on routine use in intubated infants
Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure

Table 1. Primary and Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Inhaled Nitric Oxide (N=109)</th>
<th>Placebo (N=101)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or bronchopulmonary dysplasia‡</td>
<td>25 (23)</td>
<td>19 (19)</td>
<td>1.11 (0.88–1.39)</td>
<td>0.26</td>
</tr>
<tr>
<td>Death</td>
<td>23 (21)</td>
<td>19 (19)</td>
<td>1.08 (0.86–1.35)</td>
<td>0.11</td>
</tr>
<tr>
<td>Bronchopulmonary dysplasia</td>
<td>96 (88)</td>
<td>76 (75)</td>
<td>1.03 (0.83–1.27)</td>
<td>0.68</td>
</tr>
<tr>
<td>Grade 2 or 3 ROP or IVH</td>
<td>53 (49)</td>
<td>59 (58)</td>
<td>0.89 (0.69–1.14)</td>
<td>0.36</td>
</tr>
</tbody>
</table>

Inhaled Nitric Oxide for Premature Infants with Severe Respiratory Failure

Table 2. Post-Hoc Analysis According to Birth Weight, Type of Ventilation, and Oxygenation Index

<table>
<thead>
<tr>
<th>Variable</th>
<th>Inhaled Nitric Oxide</th>
<th>Placebo</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth weight, g</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;1000</td>
<td>135 (123)</td>
<td>129 (119)</td>
<td>1.04 (0.86–1.25)</td>
<td>0.73</td>
</tr>
<tr>
<td>1001 to 1500</td>
<td>24 (21)</td>
<td>19 (19)</td>
<td>1.08 (0.87–1.33)</td>
<td>0.41</td>
</tr>
<tr>
<td>1501 to 2000</td>
<td>11 (10)</td>
<td>8 (8)</td>
<td>1.00 (0.73–1.36)</td>
<td>1.00</td>
</tr>
<tr>
<td>Grade 2 or 3 ROP or IVH</td>
<td>54 (49)</td>
<td>63 (62)</td>
<td>0.87 (0.69–1.09)</td>
<td>0.20</td>
</tr>
<tr>
<td>Mechanical ventilation</td>
<td>115 (105)</td>
<td>98 (98)</td>
<td>1.10 (0.91–1.32)</td>
<td>0.37</td>
</tr>
<tr>
<td>Other ventilation</td>
<td>16 (14)</td>
<td>10 (10)</td>
<td>1.52 (0.92–2.49)</td>
<td>0.12</td>
</tr>
</tbody>
</table>

NIH Consensus Conference Statement: Inhaled Nitric-Oxide Therapy for Premature Infants

- "The available evidence does not support use of iNO in early-outcome, early-rescue, or later-rescue regimens in the care of premature infants of <34 weeks’ gestation who require respiratory support.

- There are rare clinical situations, including pulmonary hypertension or hypoplasia, that have not been inadequately studied in which iNO may have benefit in infants of <34 weeks’ gestation. In such situations, clinicians should communicate with families regarding the current evidence on its risks and benefits as well as remaining uncertainties.

Use of Inhaled Nitric Oxide in Preterm Infants

AAP Committee on Fetus and Newborn

- “The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicated that neither rescue nor routine use of iNO improves survival with respiratory failure” (Evidence quality, A, grade of recommendation, strong)
Infants after Prolonged Preterm Rupture of Membranes (PPROM) with respiratory failure

- Decreased proinflammatory cytokines and nitrite + nitrate levels were low, but increased during iNO treatment (Askie et al. J Pediatr 2012;161:397)
  - Suggesting that there may be a transient deficiency in the inflammatory response including a defect in nitric oxide generation in the airspaces.

Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of RCTs (MAPPINO)

- Significant heterogeneity in patient populations between trials and within trials
- Individual patient data Meta-analysis provides more uniformity
- Data from 3298 infants in 12 trials

Inhaled Nitric Oxide in Preterm Infants: An Individual-Patient Data Meta-analysis of RCTs (MAPPINO)

- Conclusions:
  - Routine use of iNO for treatment of respiratory failure in preterm infants cannot be recommended.
  - The use of a higher starting dose might be associated with improved outcome, but because these were differences in the designs of these trials, it requires further examination.

Off-Label Use of Inhaled Nitric Oxide After Release of NIH Consensus Statement

- iNO use in preterm infants 23-29 wks GA: 5.03% to 6.19% (23% increase)
Off-Label Use of Inhaled Nitric Oxide After Release of NIH Consensus Statement

Inhaled Nitric Oxide for the Preterm Infant: Evidence vs. Practice

• Three possibilities
  — Lack of awareness of the evidence (-)
  — Neonatologists’ view that the evidence may not be generalizable in a particular situation (+)
  — Neonatologists’ instinct to attempt to normalize physiology (++)
• Need for focused trials
  — iNO on preterm infants with evidence of PH (robust entry criteria using ABG, echo…)
  — iNO in preterm infants after PPROM
• Some questions may be answered using large databases
  — Call for registering patients undergoing off-label treatment to databases such as the existing “European Inhaled Nitric Oxide Registry” (www.medicnet.net/ino)

Conclusions

• No routine use of iNO in preterm infants with respiratory failure
• Individualized approach
  — Severe hypoxic respiratory failure (based on applied pathophysiology)
    • PPHN should be proven (by echocardiography) in preterm infants
    • Preterm infants born after PPROM?
    • Preterm infants with early onset sepsis?
• Parents should be informed/involved if iNO is used in preterm infants
• Patients should be treated within the context of RCTs and/or registered in a database
  — Database should include long-term outcomes

Thank you very much!