Use of Inhaled Nitric Oxide Therapy in the Preterm Population

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University of Colorado
Children’s Hospital - Colorado

Faculty Disclosure

John P. Kinsella

Mallinckrodt: honorarium, grant support

“Off-label” use disclosure relevant to my presentation:
Inhaled NO in premature newborns
Inhaled Nitric Oxide Therapy in PPHN


ELSO Database: Neonatal Respiratory ECMO

ELSO International Summary – Jan. 2011
Inhaled NO in Premature Newborns: Overview

- Review the rationale for the use of inhaled nitric oxide in premature newborns.
- Summarize the results of clinical trials of iNO in premature newborns for prevention of BPD.
- Consider potential trials for less common conditions in premature newborns.

NOS Modulates Basal PVR in the Premature Fetus

Kinsella JP and Abman SH, 1996
iNO in the Premature Lung

- iNO improves gas exchange, decreases PVR, and decreases lung neutrophil accumulation in the mechanically ventilated premature lamb with RDS. (Kinsella et al, 1994, 1997)
- In the premature baboon, iNO improves early pulmonary function and favorably alters extracellular matrix deposition. (McCurnin et al, 2005)
- iNO enhances distal lung growth in newborn animals exposed to hyperoxia (Lin et al, 2005) and mechanical ventilation (Bland et al, 2005).
**Lung Injury: Pathogenesis of BPD**

- **Mechanical Ventilation**
- **Oxygen Toxicity**
- **Lung Inflammation**

**Acute Lung Injury: Birth → 2 Weeks**
- VEGF-NO Dyshomeostasis
- Inhibition of alveolarization and vascular growth

**BPD**
- Prolonged ventilator and supplemental oxygen support
- Late cardio-pulmonary sequelae
- Morbidity associated with late infections
- Late cardio-pulmonary sequelae

**Pathogenesis of BPD**

- **Mechanical Ventilation**
- **Oxygen Toxicity**
- **Lung Inflammation**

**Acute Lung Injury: Birth → 2 Weeks**
- Inhibition of alveolarization and vascular growth

**BPD**
- Prolonged ventilator and supplemental oxygen support
- Prolonged hospitalization
- Morbidity associated with late infections
- Late cardio-pulmonary sequelae
RCT of low-dose iNO in Premature Newborns with Severe HRF

- Hypothesis: iNO (5 ppm) would improve survival without ↑ in bleeding complications.
- Multicenter RCT: 12 centers
- < 34 wks gestation, < 7d
- a/\(AO_2\) ≤ 0.10
- N = 80

(Kinsella et al, Lancet 354:1061-5; 1999)

Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Control (N=32)</th>
<th>iNO (N=48)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>15 (47%)</td>
<td>25 (52%)</td>
<td>0.65</td>
</tr>
<tr>
<td>CLD</td>
<td>12 (80%)</td>
<td>15 (60%)</td>
<td>0.29</td>
</tr>
<tr>
<td>D/C on (O_2)</td>
<td>12 (80%)</td>
<td>13 (54%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Vent. days</td>
<td>37 (8-395)</td>
<td>26 (3-69)</td>
<td>0.046</td>
</tr>
</tbody>
</table>
Intracranial Hemorrhage

iNO in Premature Infants with RDS

- Randomized, double-blind, placebo-controlled trial
- Single site: The University of Chicago, Children’s Hospital
- Randomized: Inhaled NO or placebo
- Randomized: Conventional ventilation or HFOV

Schreiber, MD et al; NEJM, 349:2099;2003
Incidence (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=101)</th>
<th>Inhaled NO (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>22 (22%)</td>
<td>17 (16%)</td>
</tr>
<tr>
<td>BPD</td>
<td>42 (42%)</td>
<td>35 (33%)</td>
</tr>
<tr>
<td>Death</td>
<td>64 (64%)</td>
<td>52 (49%)</td>
</tr>
</tbody>
</table>

OR: 0.56
95% CI: 0.32-0.97
*p = 0.04

Schreiber, MD et al; NEJM, 349:2099;2003

Incidence (%)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Placebo (n=101)</th>
<th>Inhaled NO (n=106)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVL</td>
<td>13 (12%)</td>
<td>5 (5%)</td>
</tr>
<tr>
<td>Grade IV</td>
<td>13 (13%)</td>
<td>6 (6%)</td>
</tr>
<tr>
<td>Grade III</td>
<td>5 (5%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

OR: 0.45
95% CI: 0.21-0.94
*p = 0.03

Schreiber, MD et al; NEJM, 349:2099;2003
NICHD Neonatal Network Study

Primary Aim: To determine whether iNO decreases incidence of CLD/death in premature newborns

Van Meurs et al, NEJM, July, 2005

Study Subjects and Dose

- 401-1500 grams; <34 weeks GA
- Age 4-120 hours
- 5-10 ppm dose response:
  gas discontinued if <10 torr increase in PaO2
Results

• 420 patients randomized
• Mean OI = 22-23
• iNO treatment duration = 39h (C); 76h (iNO)
• Overall No differences in:
  – Mortality, BPD, ICH
• Post Hoc analyses:
  – Decreased incidence of death/BPD in group > 1k
    • 69% Control vs. 50% iNO
  – Increased incidence of ICH in group ≤ 1kg

iNO in Mechanically Ventilated Preterm Infants at 7-21 Days

• Primary aim: To determine whether iNO increases survival without CLD in premature newborns requiring mechanical ventilation at 7-21 days of age.

Ballard R, et al; NEJM 2006
### Inclusion Criteria

- 500 - 1250 gm
- Between 7 and ≤ 21 days old

### Primary Outcome

At 36 wk PMA

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>PBO</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td>N=294</td>
<td>N=288</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>SURVIVED w/o CLD</td>
<td>43.9%</td>
<td>36.8%</td>
</tr>
</tbody>
</table>

Relative Risk (Benefit) (95% CI) 1.23 (1.01, 1.51)

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>HAD CLD</td>
<td>56.1%</td>
<td>63.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIED (n)</td>
<td>16</td>
<td>18</td>
</tr>
</tbody>
</table>
**“Earlier” Enrollment More Effective**

<table>
<thead>
<tr>
<th></th>
<th>INO</th>
<th>PBO</th>
<th>P=</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TOTAL GROUP</strong></td>
<td>N=294</td>
<td>N=288</td>
<td></td>
</tr>
<tr>
<td><strong>EARLY ENTRY</strong></td>
<td>N= 112</td>
<td>N= 115</td>
<td></td>
</tr>
<tr>
<td>(7-14D)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*SURVIVED w/o CLD</td>
<td>49.1%</td>
<td>27.8%</td>
<td>0.001</td>
</tr>
<tr>
<td>(P=0.006 by entry treatment interaction)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>*DIED (n)</td>
<td>11</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

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**Early Inhaled Nitric Oxide in Premature Newborns with Respiratory Failure:**

**NHLBI UO1-64857**

- We hypothesized that low-dose iNO (5 ppm) would decrease the incidence of death/BPD in mechanically ventilated premature newborns, without increasing the risk of adverse events (ICH).

*Kinsella JP, et al; NEJM 2006*
Study Design

- Multicenter, RCT of iNO treatment in premature newborns who required mechanical ventilation in the first 48 hours after birth.
- iNO continued for 21 days or until extubation.
- Enrollment was stratified in 250 g increments by birthweight (500-1250 g)
- 793 newborns were enrolled between 3/01 and 6/05.

Mortality by Treatment Group

<table>
<thead>
<tr>
<th>Group</th>
<th>iNO</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>N</td>
<td></td>
</tr>
<tr>
<td>500-749</td>
<td>55 (29)</td>
<td>66 (35)</td>
<td>0.20</td>
</tr>
<tr>
<td>750-999</td>
<td>15 (11)</td>
<td>24 (17)</td>
<td>0.13</td>
</tr>
<tr>
<td>1000-1250</td>
<td>8 (12)</td>
<td>8 (13)</td>
<td>0.97</td>
</tr>
<tr>
<td>Total</td>
<td>78 (20)</td>
<td>98 (25)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
## BPD by Treatment Group

<table>
<thead>
<tr>
<th>Group</th>
<th>iNO</th>
<th>Control</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-749</td>
<td>113 (78)</td>
<td>100 (76)</td>
<td>0.59</td>
</tr>
<tr>
<td>750-999</td>
<td>82 (66)</td>
<td>76 (63)</td>
<td>0.71</td>
</tr>
<tr>
<td>1000-1250</td>
<td>17 (30)</td>
<td>34 (60)</td>
<td>0.001</td>
</tr>
<tr>
<td>Total</td>
<td>212 (65)</td>
<td>210 (68)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

**Incidence (%)**

RR: 0.73  
95% CI: .55-.98  
* p = 0.032

## Low Dose iNO Decreases Brain Injury in Premature Newborns

![Bar chart showing incidence of brain injury by group with statistical significance.](chart.png)
### Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>iNO</th>
<th></th>
<th>Control</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>%</td>
<td>N</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>PDA – Medical Tx</td>
<td>215</td>
<td>(54)</td>
<td>212</td>
<td>(53)</td>
<td>0.27</td>
</tr>
<tr>
<td>PDA – Ligation</td>
<td>86</td>
<td>(21)</td>
<td>86</td>
<td>(22)</td>
<td>0.51</td>
</tr>
<tr>
<td>Pulmonary Hem.</td>
<td>24</td>
<td>(6.1)</td>
<td>26</td>
<td>(6.6)</td>
<td>0.75</td>
</tr>
<tr>
<td>Threshold ROP</td>
<td>66</td>
<td>(17)</td>
<td>60</td>
<td>(15)</td>
<td>0.59</td>
</tr>
<tr>
<td>NEC</td>
<td>53</td>
<td>(14)</td>
<td>46</td>
<td>(13)</td>
<td>0.54</td>
</tr>
<tr>
<td>Air Leak</td>
<td>25</td>
<td>(6.3)</td>
<td>24</td>
<td>(6.1)</td>
<td>0.90</td>
</tr>
</tbody>
</table>

### Summary

- Inhaled NO did not decrease the incidence of death/BPD for infants with BW 500-1250 g. However, iNO reduced the incidence of BPD in infants with BW >1000 g by 50%.
- Inhaled NO decreased the incidence of brain injury in infants with BW 500-1250 g, without increasing other adverse events.
Inhaled NO the Premature Newborn: Summary of Clinical Trials

- 12 RCTs, 3298 infants
- No significant effect of iNO on:
  - death or CLD
  - severe neurologic events

Early Treatment (< 3 days) as Prophylaxis

- Kinsella et al, NEJM 2006
  - Neuroprotection demonstrated for infants 500-1250 grams
  - Decreased BPD by 50% in 1000-1250 g subset
- EUNO (Ikaria), Lancet, 2010
  - No evidence of neuroprotection or BPD reduction
### Late Treatment for Evolving BPD (> 5 days)

- **Ballard et al, NEJM 2006**
  - BPD reduction (63% vs 56%)
  - Most benefit from treatment at 7-14 days
- **NewNO Trial (Ikaria), Yoder et al, 2013**
  - No BPD reduction

### Inhaled NO in the Premature Newborn: Summary of Clinical Trials

- Conflicting results from large MCTs for both early iNO (<72 hours after birth), and late treatment for evolving BPD (>5d).
- Meta-analyses and consensus statements do not support the use of iNO to prevent BPD.
Consensus Statements

• The use of iNO to prevent BPD is not supported by the available evidence.
  – NIH Consensus Development Conference
  – AAP Committee on the Fetus and Newborn

Non-Invasive Inhaled Nitric Oxide in Premature Newborns


University of Colorado School of Medicine, University of Alabama – Birmingham, Northwestern, Nationwide Children’s, Vanderbilt, UCSD

HL084923
Hypothesis

- Non-invasive iNO will reduce the combined endpoint of BPD/mortality in premature newborns (500-1250 grams birth weight, <72 hours) who are not mechanically ventilated at the time of enrollment.

Death and/or BPD by Treatment Group

<table>
<thead>
<tr>
<th>Group</th>
<th>iNO N=59</th>
<th>Control N=65</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>500-749</td>
<td>3 (30)</td>
<td>5 (56)</td>
<td>0.66</td>
</tr>
<tr>
<td>750-999</td>
<td>9 (53)</td>
<td>6 (29)</td>
<td>0.16</td>
</tr>
<tr>
<td>1000-1250</td>
<td>13 (41)</td>
<td>15 (44)</td>
<td>0.77</td>
</tr>
<tr>
<td>Total</td>
<td>25 (44)</td>
<td>26 (42)</td>
<td>0.86</td>
</tr>
</tbody>
</table>
Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>iNO</th>
<th>Control</th>
<th>P</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N=59</td>
<td>N=65</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical Ventilation</td>
<td>13 (22)</td>
<td>15 (23)</td>
<td>0.89</td>
<td>0.97 (0.62-1.52)</td>
</tr>
<tr>
<td>NEC</td>
<td>5 (9)</td>
<td>10 (16)</td>
<td>0.23</td>
<td>0.54 (0.20-1.49)</td>
</tr>
<tr>
<td>PDA Tx</td>
<td>4 (7)</td>
<td>10 (15)</td>
<td>0.27</td>
<td>0.62 (0.27-1.46)</td>
</tr>
<tr>
<td>ICH 3-4</td>
<td>2 (3)</td>
<td>4 (6)</td>
<td>0.68</td>
<td>0.69 (0.22-2.17)</td>
</tr>
<tr>
<td>Sepsis</td>
<td>13 (22)</td>
<td>14 (22)</td>
<td>0.95</td>
<td>1.01 (0.52-1.96)</td>
</tr>
</tbody>
</table>

Conclusions

- Although demonstrated to be safe in this pilot trial, non-invasive iNO did not decrease the incidence of death/BPD for infants with BW 500-1250 g.
- Secondary outcomes were not different between the two groups.
Conclusions

• Over 2 decades, ~ 4800 premature newborns have been enrolled in 17 RCTs
• Although benefit in subsets, no consistent signal for BPD reduction
• iNO does not increase the risk of ICH, PDA or other secondary outcomes

Unstudied Conditions in Premature Newborns

• Insufficient data for subsets of infants:
  – PPHN in premature newborns with pulmonary hypoplasia
  – BPD with acute deterioration
  – Chronic therapy for newborns with BPD and PH
PPHN Focus in 2017

- Premature newborns with PPHN
  - Focus on BPD in the past
  - Multiple reports show that PPHN in premature newborns in the first days of life responds to pulmonary vasodilator therapy similar to the term newborn

PPHN in the Premature Newborn

- Peliowski et al, 1995, J Pediatrics
- 8 premature newborns 24-31 weeks gestation with prolonged rupture of membranes and oligohydramnios, PPHN
- All with marked improvement in oxygenation
- 6/8 survived
PPHN in the Premature Newborn

• Chock et al, Am J Perinatol, 2009
• Subset of NICH NRN trial
• 12 premature newborns with PPROM, oligohydranmnios and pulmonary hypoplasia
• 6 in iNO group, 6 in control group
• 33% mortality in iNO group vs 66% mortality in the control group

PPHN in the Premature Newborn

• Shah and Kluckow, J Paed Child Health, 2011
• Premature newborns (28 weeks) with PPROM, pulmonary hypoplasia and PPHN
• Survival improved from 62% to 90% after the introduction of iNO and high frequency oscillatory ventilation in the management.
PPHN in the Premature Newborn

• Semberova et al, J Perinatol, 2015
• 22 premature newborns with PPROM, pulmonary hypoplasia and PPHN
• 86% survival rate with iNO treatment

PPHN in the Premature Newborn

• Common to all of these reports is severe hypoxemic respiratory failure and PPHN presenting in the first day of life and showing marked improvement in oxygenation after treatment with iNO; similar to the response typical for the term newborn with idiopathic PPHN.
RCT of iNO for PPHN in the Premature Newborn?

- A proper RCT of iNO in premature newborns with severe PPHN physiology has not been done.
- Unlike the term newborn, no rescue strategy (ECMO). Outcome would be survival.
- Lack of equipoise.

PPHN in the Premature Newborn

- Are we treating PPHN in premature newborns?
  - Would you treat a 33 week gestation infant with PPHN physiology with a selective pulmonary vasodilator?
  - Current management is unknown (treatment with iNO, inhaled Flolan, no specific drug therapy)
  - Prospective registry to determine current practice in the US.
Recommendations

• Inhaled NO therapy should not be used in premature infants for the prevention of BPD.
• iNO can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung disease.
• iNO is preferred over other pulmonary vasodilators in preterm infants based on a strong safety signal from short and long-term follow-up of large numbers of patients from multicenter RCTs.

Kinsella et al, J Pediatr, 2016