Yes or No: Use of iNO in Preterm Infants

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The speaker has disclosed that (1) he will discuss the off-label use of inhaled nitric oxide during this presentation; (2) he is a University of Texas at Houston Principal Investigator of a research study partially funded by Ikaria, Inc. (TOLSURF Trial, R. Ballard, PI). He has no significant financial interest or relationship with the companies or the manufacturer(s) of any other commercial product and/or service that will be discussed as part of this presentation.

Session Summary

Inhaled nitric oxide is a mainstay of therapy in late preterm and term infants with hypoxic respiratory failure. The role of iNO in the preterm infant remains less clear. In this talk the speaker will review randomized trials of iNO in preterm infants and discuss its potential role in management of respiratory failure and in the prevention of BPD.

Session Objectives

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

- understand the mechanism of action of iNO;
- discuss potential effects of iNO on lung development;
- review and understand trials of iNO in preterm infants, including:
  - early rescue
  - early prophylactic
  - late therapy

References


**Session Outline**

See presentation handout on the following pages.
The Use of Inhaled Nitric Oxide in Preterm Infants: Yes or NO?

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Houston, TX

Disclosures
• This talk will discuss off label use of inhaled nitric oxide
• Dr. Eichenwald is UT Houston PI of research study partially funded by Ikaria, Inc. (TOLSURF Trial, R. Ballard, PI)

Objectives
• Understand mechanism of action of iNO
• Discuss potential effects of iNO on lung development
• Review trials of iNO in preterm infants
  – Early rescue
  – Early prophylactic
  – Late therapy

Use of iNO in Preterm Infants?

Use of iNO in Preterm Infants?

a) 25 week 750 g 6-hour old infant: HFOV and PIE with Oxygenation Index of 22

b) 28 week 1150 g infant 36 hours old: SIMV 20/5x30, 0.35 O₂

Use of iNO in Preterm Infants?

a) 25 week 750 g 6-hour old infant: HFOV and PIE with OI 22  (Van Meurs, 2005)

b) 28 week 1150 g infant 36 hours old:
  SIMV 20/5x30, 0.35 O₂  (Schreiber, 2003; Kinsella, 2006)

c) 25 week 780 g infant 10 days old on CPAP, 0.40 O₂  (Ballard, 2006)

Primary outcome: Survival without bronchopulmonary dysplasia

Nitric Oxide

• Naturally occurring molecule
• Regulates vascular tone (cell signaling)
• Gas exogenously administered to lung: potent pulmonary vasodilator
• Reduces the need for ECMO in late preterm and term infants with PPHN
Potential Effects of iNO on Lung

**Potential Benefits of iNO in Preterm Lung**

<table>
<thead>
<tr>
<th>Short Term</th>
<th>Long Term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pulmonary vasodilatation</td>
<td>Reduction in oxidant stress</td>
</tr>
<tr>
<td>Improved V/Q matching</td>
<td>Improved surfactant function</td>
</tr>
<tr>
<td>Reduction in inflammation and neutrophil accumulation</td>
<td>Improved alveolarization</td>
</tr>
<tr>
<td></td>
<td>Reduced vascular remodeling and improved vascular growth</td>
</tr>
</tbody>
</table>

Rationale for Use in Preterm

- Respiratory Distress Syndrome has some component of pulmonary hypertension
- iNO may improve V/Q mismatch
- iNO has other effects on airway resistance and surfactant function
- May affect lung development

iNO improves lung compliance and expiratory resistance in baboon model of CLD

iNO improves pressure-volume curves in baboon model

iNO improves lung growth


**Potential Toxicities of iNO**

- Methemoglobinemia
- Platelet dysfunction
- Generation of NO₂
- Unknown additional toxicities in preterm infants?

**Studies of iNO in Preterm Infants**

- Multiple randomized, masked trials
- Major differences in iNO treatment protocol:
  - Timing
  - Dose
  - Duration
  - Population

**iNO Studies in Preterm Infants are Heterogeneous**

- Early rescue
  - Oxygenation index criteria
    - Less than 48 hours old, ventilated
    - Schreiber, NEJM 2003; Kinsella, NEJM 2006

- Early prophylactic or “routine”
  - Less than 48 hours old, ventilated

- Late therapy for “at risk” infants
  - Infants at high risk for BPD
    - Ballard, NEJM 2006

**Early Rescue with iNO**

- Less than 34 weeks, BW 401-1500 g
- Oxygenation index ≥ 10 (revised in study)
- Eligible from 4 to 120 hours of age
- Initial dose 5 ppm (increase to 10 ppm); weaned every 4 – 8 hrs
- “Responders” defined as increase in PaO₂ by 20 mm Hg at 30 minutes

**Clinical Characteristics**

<table>
<thead>
<tr>
<th></th>
<th>iNO N=210</th>
<th>Placebo N=210</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>840 ± 264</td>
<td>837 ± 260</td>
</tr>
<tr>
<td>Gest Age (wk)</td>
<td>26 ± 2</td>
<td>26 ± 2</td>
</tr>
<tr>
<td>Age (hrs)</td>
<td>26 ± 23</td>
<td>28 ± 22</td>
</tr>
<tr>
<td>OI</td>
<td>23 ± 17</td>
<td>22 ± 17</td>
</tr>
<tr>
<td>Duration gas (hrs)</td>
<td>76 ± 73</td>
<td>39 ± 65*</td>
</tr>
</tbody>
</table>

**Major Outcomes**

<table>
<thead>
<tr>
<th></th>
<th>iNO N=210</th>
<th>Placebo N=210</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or BPD</td>
<td>80 %</td>
<td>82 %</td>
<td>0.52</td>
</tr>
<tr>
<td>Death</td>
<td>52</td>
<td>44</td>
<td>0.11</td>
</tr>
<tr>
<td>BPD</td>
<td>60</td>
<td>68</td>
<td>0.26</td>
</tr>
<tr>
<td>Grade ¾ IVH/PVL</td>
<td>39</td>
<td>32</td>
<td>0.11</td>
</tr>
<tr>
<td>Severe ROP</td>
<td>30</td>
<td>32</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Major Outcomes by Birth Weight

Late iNO in At Risk Infants

- Multicenter, randomized masked trial
- Less than 32 weeks, 500 – 1,250 g
- Mechanical ventilation or CPAP (< 800 g) at 7 – 21 days
- Initial dose 20 ppm x 72 hours, weaned weekly (24 days total therapy)


Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>iNO N=294</th>
<th>Placebo N=288</th>
</tr>
</thead>
<tbody>
<tr>
<td>Birth Weight (g)</td>
<td>766 ± 161</td>
<td>759 ± 155</td>
</tr>
<tr>
<td>Gest Age (wk)</td>
<td>26 ± 1.5</td>
<td>26 ± 1.5</td>
</tr>
<tr>
<td>Age (days)</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>RSS</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Duration gas</td>
<td>24 days</td>
<td>24 days</td>
</tr>
</tbody>
</table>


Major Outcomes

<table>
<thead>
<tr>
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<th>iNO N=294</th>
<th>Placebo N=288</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or BPD</td>
<td>56.1 %</td>
<td>63.2 %</td>
<td>0.04</td>
</tr>
<tr>
<td>Death</td>
<td>5.4</td>
<td>6.3</td>
<td>NS</td>
</tr>
<tr>
<td>D/C @ 40 w PMA</td>
<td>42.5</td>
<td>34</td>
<td>0.01</td>
</tr>
<tr>
<td>D/C @ 44 w PMA</td>
<td>79.3</td>
<td>69.1</td>
<td>0.03</td>
</tr>
</tbody>
</table>


Survival without BPD

Other Findings

- Less severe BPD with iNO
- No acute change in pulmonary mechanics
- Less use of bronchodilators at 12 months
- Cost effectiveness
- No difference in developmental outcomes
- No evidence for other toxicities, ?improved surfactant function

Questions?

- Trial selected out infants who survived first week
- Is iNO most effective in infants at high risk to develop BPD when started earlier?
- Is there a racial difference in iNO effects?
- Does longer therapy at higher dose provide additional benefit?
Risk Factors for PH in Preterm Infants
- Fetal growth restriction
- Prolonged premature rupture of membranes with pulmonary hypoplasia
- Early onset sepsis
- Oligohydramnios
- Late PH with bronchopulmonary dysplasia

PaO₂ Response in Preterm Infants with PH

Response to iNO Dependent on Gestational Age

iNO use in Premature in 37 US Children’s Hospitals
Pulmonary Hypertension in ELBW
- Prospective evaluation in 145 ELBWs in single center
- Echocardiogram at 4 weeks, later if severe lung disease
- 18% diagnosed with PH (6% early)
- Risk factors:
  - Small for gestational age
  - More severe BPD (higher oxygen need)

Bhat R et al., Pediatrics 2012

Outcomes of Severe PH in BPD

Response of Infants with BPD to iNO


So what do we know?
- No benefit of early, low dose iNO in ELBW
- iNO may affect lung development and decrease risk of BPD in some patients
  - May be dependent on dose, duration and timing
- iNO may increase risk of death or brain injury if used in critically ill ELBW
  - Should discourage iNO as last ditch rescue

So what should we do?
- Recommend iNO as adjunct therapy for prevention of BPD only in clinical trials
- Use early (rescue) iNO only in preterm infants with documented severe pulmonary hypertension (PROM, pulmonary hypoplasia)
- Discourage use in ELBWs with hypoxic respiratory failure due to severe lung disease
- Need for randomized trials of vasodilators in BPD patients to assess efficacy and outcomes
Questions?