USE OF INHALED NITRIC OXIDE IN THE NICU

East Bay Newborn Specialists Guideline
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iNO for Late Preterm and Term Infants with Severe PPHN

Background:
Safety and efficacy of iNO in treatment of late preterm and term infants with PPHN is supported by two large randomized trials and is recognized by the FDA as an approved treatment.

Eligibility:
Patients can be started on iNO according to this Guideline if they meet all of the following

- Gestation $\geq$ 34 weeks
- Age $\leq$ 7 days
- OI $\geq$ 25
- Clinical and echocardiographic evidence of pulmonary hypertension despite optimal respiratory support, circulatory support, and sedation

Additional considerations:

- Infants with pulmonary atelectasis due to parenchymal lung disease are unlikely to respond to iNO unless lung inflation is optimized which may include use of HFOV and/or surfactant
- Correction of transient hypothermia, electrolyte imbalance, hypoglycemia and intravascular volume is essential. (Note: Patients with HIE who are receiving therapeutic hypothermia are at risk for escalation of their pulmonary hypertension. In these cases, the potential benefit of prevention of continuing brain injury must be weighed against the risk of severe pulmonary hypertension requiring ECMO. These cases should be discussed with the ECMO attending on a case by case basis and preparations should be made to provide ECMO if necessary. During transport, it may be necessary to lower the patient's temperature only to 35 degrees C° to prevent a hypertensive crisis en route.
- Infants with severe RV dysfunction may need to be started on PGE1 to give a "pop-off" for the right ventricle at the ductus.
- Consider treatment with vasoactive substances that increase cyclic AMP (e.g. prostacyclin) and phosphodiesterase inhibitors (e.g. milrinone, sildenafil)
- iNO is contraindicated in infants with severe LV dysfunction who are dependent on a right to left shunt to maintain systemic output
- iNO should be used with caution in infants with pulmonary venous hypertension since an increase in pulmonary blood flow can result in severe pulmonary edema

Initial Rx:

- Begin iNO at 20 ppm. Higher doses provide no additional benefit and may increase toxicity
- Continue at 20 ppm for at least 4 hrs

Early Weaning:

- Begin iNO weaning after 4 hours if FiO2 < 0.6 from 20ppm to 10ppm to 5 ppm. The response to iNO is non-linear. Incremental weaning down to 5ppm is generally well tolerated and can be achieved by 24 hrs.
- iNO should be increased to the previous effective dose if the FiO2 requirement increases by > 10% within an hour after a weaning attempt
- If a patient cannot be weaned to 5 ppm iNO due to hypoxemia, consider underlying causes for ongoing hypoxic pulmonary failure; may need to consider other pulmonary vasodilators (e.g., sildenafil) or ECMO.

Weaning from 5 ppm:

- If FiO2 remains ≤0.6, iNO is discontinued from either 5ppm or 1 ppm, depending on the ease of weaning. If weaning has been difficult to this point consider subsequent hourly decrements of 1ppm (5, 4 ,3, 2, 1, and off).
- The FiO2 usually needs to be increased by 10% with final discontinuation of iNO to prevent rebound hypoxemia
- PaO2 target range is 50-80 mmHg with a SpO2 target of 90-95%. Aiming for higher PaO_2 concentrations may lead to increased ventilator support and barotrauma. Extreme hyperoxia leading to the formation of reactive oxygen radicals may be toxic to the developing lung and may worsen any underlying brain injury.
- Most patients should be off iNO within 5 days of starting, regardless of OI, FIO2, or echo findings. If a patient cannot be weaned to off iNO by 5 days of age due to hypoxemia, consider underlying causes for ongoing hypoxic pulmonary failure; may need to consider other pulmonary vasodilators (e.g., sildenafil); may need to consider ECMO.

Methemoglobin Levels:

- Check methemoglobin prior to starting iNO and 24 hours after starting iNO
- Further methemoglobin levels needed only if levels ≥ 3%
- If metHgb is > 5%, begin iNO wean

Target SPO2 range for most term and near-term patients on iNO:

- Pre-ductal SPO2 90-95%

References:

- The Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide in full-term and nearly full-term infants with hypoxic respiratory failure. NEJM 1997;336:597-604
- Clark, et al. Low dose nitric oxide therapy for persistent pulmonary hypertension of the newborn. NEJM 2000; 342:469-474
- Finer, et al. Nitric oxide for respiratory failure in infants born at or near term. Cochrane Database of Systemic Reviews 2006 Issue no. 4. Art. No. CD000399
- Davidson, et al. Safety of withdrawing inhaled nitric oxide therapy in persistent pulmonary hypertension of the newborn. Pediatrics 1999; 104:231-236

iNO for Late Preterm and Term Infants with Congenital Diaphragmatic Hernia and Respiratory Failure

Infants with CDH may or may not have a response to iNO. Transient improvement in oxygenation may be seen and can be used in stabilizing the infant while preparing for ECMO. Occasional infants may demonstrate a sustained response. Poor LV function seen in infants with CDH may account for the poor response to iNO. A single RCT of iNO in CDH and post hoc analyses from two other large RCTs showed no improvement in survival or reduction in the need for ECMO in this population.

Recommendations:

- A trial of iNO may be appropriate in infants with CDH
- iNO should be started only after providing appropriate respiratory and hemodynamic support
- Use of a more gentle ventilation strategy is recommended (maintain preductal PaO_2 at 50-70 mm Hg and $PaCO_2$ at less than 60 mm Hg)

References:

- Neonatal Inhaled Nitric Oxide Study Group. Inhaled nitric oxide and hypoxic respiratory failure in infants with congenital diaphragmatic respiratory failure. Pediatrics 1997; 99:838-45
- Kinsella, et al. Randomized, multicenter trial of inhaled nitric oxide and high-frequency oscillatory ventilation in severe, persistent pulmonary hypertension of the newborn. J Pediatr 1997;131:55-62
- Kinsella, et al. Clinical responses to prolonged treatment of persistent pulmonary hypertension of the newborn with low doses of nitric oxide. J Pediatr 1993;123:103-8

iNO for Older Preterm Infants with Severe BPD and Pulmonary Hypertension

Infants with severe BPD have varying degrees of pulmonary hypertension. Those with the most severe disease may develop progressive pulmonary hypertension, biventricular hypertrophy, and eventual RV failure. There is limited evidence of short-term improvement in oyxgenation, but no data regarding long term outcome. They are often unable to wean off iNO for long periods. Sildenafil or other pulmonary vasodilators may offer similar benefits.

Recommendations:

- There is limited evidence to support efficacy or safety of iNO and/or sildenafil in this population
- If iNO is used, it should be continued only when there is a clear response and the lowest effective dose should be given
- In iNO responders, a transition to sildenafil should be attempted and iNO should be weaned periodically with a goal to discontinue. The best way to do this is unknown. Based on anecdotal evidence, a starting dose of sildenafil using 0.5mg/kg/dose every 6 hours and increasing to a maximum dose of 1mg/kg/dose every 6 hours based on clinical and echocardiographic response is suggested. Increased toxicity has been reported in children treated with greater than 4 mg/kg/day.
- Consult the cardiology and pulmonary services at CHO
- Consider consultation with the pulmonary hypertension group at UCSF

References:

- Mourani PM, et al. Pulmonary vascular effects of inhaled nitric oxide and oxygen tension in bronchopulmonary dysplasia. Am J Respir Crit Care Med 2004;170:1006-13.
- Banks BA, et al. Changes in oxygenation with inhaled nitric oxide in Severe Bronchopulmonary Dysplasia Pediatrics 1999;103;610-8.
- Steinhorn RH, et al. Intravenous sildenafil in the treatment of neonates with persistent pulmonary hypertension. J Pediatr 2009;155:841-7.e1.
- Mourani PM, et al. Effects of long-term sildenafil treatment for pulmonary hypertension in infants with chronic lung disease. J Pediatr 2009;154:379-84.

iNO for Preterm Infants with Severe Respiratory Failure (Early Rescue)

There are rare clinical situations, including babies with confirmed pulmonary hypertension due to sepsis or oligohydramnios syndrome from PPROM who may benefit from iNO. Optimizing lung volume and prevention of atelectasis in infants with severe RDS or pneumonia should be attempted prior to consideration of iNO. Both atelectasis and over distension of lungs can increase PVR. Although there may be transient improvement in oxygenation, there are no improved outcomes in several RCTs and treatment may actually place the patient at risk for impaired platelet aggregation and increase the risk of IVH. The NICHD states that "available evidence does not support the use of iNO in early routine, early rescue, or later rescue regimens in the care of premature infants < 34 weeks gestation." The NICHD states iNO may be of benefit in rare clinical situations as noted above, but that it has been inadequately studied.

Recommendations:

- iNO should be used with extreme caution in patients under 1kg
- Routine use of iNO in patients with severe RDS is not indicated and may even be contraindicated.
- A subgroup of premature babies with PPROM and pulmonary hypoplasia with pulmonary hypertension may benefit from iNO therapy, but the risk/benefit ratio is unknown
- Other aspects of care should be optimized prior to a trial of iNO
- If a patient has no response after 30 minutes of iNO, the treatment should be discontinued

References:

- Kinsella JP, et al. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: A randomized controlled trial. Lancet 1999;354:1061-5.
- Field D, et al. Neonatal ventilation with inhaled nitric oxide versus ventilator support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO multicentre randomised controlled trial. Pediatrics 2005;115:926-36.
- Hascoet JM, et al. The safety and efficacy of nitric oxide therapy in premature infants. J
- Pediatr 2005;146:318-23.
- Van Meurs KP, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. N Engl J Med 2005;353:13-22.