

Inhaled Nitric Oxide

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I. Introduction and Background

- A. Nitric oxide is a regulator of vascular tone, endogenously produced by the vascular endothelium.
- B. Studies have shown that inhaled nitric oxide (iNO) therapy causes selective pulmonary vasodilation in animal models and newborns. Multicenter randomized controlled trials have demonstrated that iNO significantly improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO) in term and near-term infants with persistent pulmonary hypertension of the newborn (PPHN).
- C. iNO is FDA approved for term and near-term infants with hypoxic respiratory failure.

II. Administration, Dosing, and Weaning Strategies for iNO in the Term Infant

- A. See “Practice Guidelines for iNO Use in Term Neonatal Respiratory Failure,” Part 3B – Respiratory.
- B. In infants diagnosed with PPHN who are persistently refractory to iNO wean, cannot be weaned from ECMO, or have rebound pulmonary hypertension after iNO or ECMO, alternative diagnoses should be considered (e.g. surfactant protein deficiencies, alveolar capillary dysplasia).

III. Other uses of iNO therapy

- A. **Congenital Diaphragmatic Hernia (CDH):** Prospective randomized controlled trials of iNO for CDH have failed to show reduced need for ECMO or reduced mortality. iNO is, nonetheless, used in CDH patients with refractory hypoxemia prior to ECMO as a rescue therapy. In addition, some CDH patients have prolonged pulmonary hypertension despite improvements in respiratory support requirements. These patients may benefit from long-term, low-dose nitric oxide—which may even be delivered by nasal cannula if mechanical ventilation is no longer required. Serial echocardiograms, assessing changes in pulmonary hypertension, should be used to assist in the management of these complex patients.
- B. **Cardiac indications:** iNO has been used for pulmonary hypertension related to cardiac anomalies, particularly in the post-operative phase. Few published data exist with regard to outcome, although iNO has been reported to reduce pulmonary artery pressure and possibly reduce the need for ECMO.
- C. **iNO for preterm infants with severe respiratory failure**
 - 1. We have recently participated in a NICHD multi-center, double-masked, randomized controlled clinical trial of iNO therapy to evaluate the use of iNO in premature infants with severe respiratory failure. This trial showed no benefit to survival or in reduction of rate of physiologic BPD in infants with severe RDS. Subgroup analysis suggested that infants >1000 g may benefit in terms of the outcome of death or BPD. However, neurodevelopment follow-up from this trial showed no benefit from iNO exposure on death or neurodevelopmental impairment, or neurodevelopmental outcomes in early childhood among the severely ill premature infants in this trial. In fact, an increased risk of moderate to severe CP was seen among survivors given iNO. Although a single-center trial showed a reduction of BPD in iNO-treated premature infants and subsequent improved neurodevelopmental outcomes in the iNO group, that cohort was substantially less ill than

the NICHD trial cohort. Other trials of iNO to premature infants have investigated the drug effect among patients with varying severity of illness and at different times in the development of chronic lung disease.

2. The use of iNO in the preterm population remains controversial. iNO has not been consistently shown to be effective in reducing rates of BPD or death. Severity of patient illness, presence of pulmonary hypoplasia, timing of initiation, and duration of therapy may all be shown to be important factors in the efficacy of iNO treatment among premature infants. Use of iNO for pre-term infants outside clinical trials should be approached with caution. Statistically higher rates of Grade 3-4 IVH or PVL were seen in infants <1000 g treated with iNO. Families should be counseled that iNO may have no long-term benefit for extremely ill, extremely low birth weight infants with severe respiratory failure, and that its use may represent an extreme and ultimate interventional attempt.
3. If iNO is to be used, it is important to note that iNO dosing strategies have not been determined for the preterm population, but it is prudent to initiate iNO at 10 ppm in preterm infants. Response to therapy should then be evaluated in the usual fashion, and an increase to 20 ppm undertaken only if no effect is noted at 10 ppm.

IV. Toxicity

- A. There are four theoretical toxicities associated with iNO use:
 1. Inhaled NO combines with oxygen to form nitrogen dioxide (NO₂), a toxic gas.
 2. Methemoglobin is formed when NO reacts with hemoglobin. Methemoglobin is incapable of transporting oxygen and levels in excess of 5-10% produce cyanosis. Premature infants have low levels of methemoglobin reductase, which make them more susceptible to methemoglobinemia. See “Practice Guidelines for Inhaled Nitric Oxide Use in Term Neonatal Respiratory Failure,” Part 3B – Respiratory.
 3. Platelet dysfunction and bleeding problems are theoretical risks, but no increases in intracranial hemorrhage rates have been documented in the iNO studies to date. No increase in the rate of severe IVH or PVL was seen in infants <1500g enrolled in the study. Subgroup analysis of infants <1000g found a higher rate of severe IVH and PVL in the iNO group.
 4. Oxidative injury is a potential risk of iNO therapy. Both NO and NO₂ are highly reactive. NO₂ both initiates lipid peroxidation and reacts with superoxide to form peroxynitrite which can cause oxidative injury.
- B. Careful monitoring of NO, NO₂, and methemoglobin levels occurs in a protocolized fashion for any infant receiving iNO. Fortunately, no serious clinical toxicity has been described with iNO therapy in newborns, likely due to meticulous monitoring.