Clinical Trials of Inhaled Nitric Oxide Therapy in the Newborn

John P. Kinsella, MD*

OBJECTIVES
After completing this article, readers should be able to:
1. Describe the benefits of inhaled nitric oxide in the treatment of persistent pulmonary hypertension of the newborn.
2. Determine the range of appropriate initial doses of inhaled nitric oxide therapy for term neonates.
3. Delineate the potential role of inhaled nitric oxide in conjunction with extracorporeal membrane oxygenation.
4. Describe the lung-specific effects of low-dose inhaled nitric oxide therapy in preterm newborns who have severe hypoxemic respiratory failure.

Introduction
Early reports of the use of inhaled nitric oxide (iNO) in term newborns who had persistent pulmonary hypertension showed both acute and sustained improvement in oxygenation. Subsequently, randomized controlled trials of iNO in term newborns confirmed that this selective pulmonary vasodilator improves oxygenation and reduces the need for extracorporeal membrane oxygenation (ECMO). Results of a more recent randomized controlled trial of iNO in term newborns corroborate the findings of previous studies. These studies should provide sufficient evidence of the safety and efficacy of iNO to support regulatory approval of this therapy for persistent pulmonary hypertension of the newborn (PPHN). However, less is known about the potential role of iNO in preterm newborns. In this review, we summarize the key findings of clinical trials in the term newborn and the current status of iNO in the preterm newborn.

iNO in Term Newborns
After the publication of pilot trials with iNO, which documented marked improvement in oxygenation in term newborns who had PPHN, several randomized, controlled trials were conducted and demonstrated further the efficacy of iNO in PPHN. For example, these studies reported acute improvement in oxygenation after 30 minutes of iNO treatment. iNO reduced the need for ECMO, and lung recruitment strategies augmented the response to iNO when PPHN complicated the course of patients who had parenchymal lung disease. However, none of the studies was designed to evaluate the efficacy of the initial dose employed, and there remains some confusion about the appropriate starting dose for term newborns who have PPHN because of the lack of appropriate dose-response studies.

APPROPRIATE DOSES
The first published experience of iNO treatment in term newborns reported initial doses ranging from 6 to 20 ppm to 80 ppm. The rationale for doses used in these clinical trials was based on concentrations that had been found to be effective in animal experiments by the same investigators. Brief (30 min) inhalation of NO at 80 ppm improved oxygenation in patients who had PPHN, but the response was not sustained in some patients after NO was discontinued. Rapid improvement in oxygenation in neonates who had severe PPHN also was demonstrated, but this was achieved at lower doses (20 ppm) administered for 4 hours, and decreasing the iNO dose to 6 ppm for the duration of treatment provided sustained improvement in oxygenation. Other studies documented the relative effectiveness of low-dose iNO in improving oxygenation in patients who had severe PPHN. Thus, acute improvement in oxygenation during treatment does not appear to vary with doses of iNO ranging from 5 to 80 ppm.

These laboratory and clinical studies established the boundaries of iNO dosing protocols for subsequent randomized, clinical trials in newborns. Increasing the dose to 40 ppm generally does not improve oxygenation among patients who do not respond to the lower dose of 20 ppm. The initial dose in the Neonatal Inhaled Nitric Oxide Study (NINOS) was 20 ppm, but the dose was increased to 80 ppm if the improvement in Pao2 was less than 20 torr. In this study, only 3 of 53 infants (6%) who had little response to 20 ppm had an increase in Pao2 of greater than 20 torr when treated with 80 ppm iNO. Whether a progressive increase in Pao2 would have occurred with continued exposure to 20 ppm could not be determined with this study design. Others initiated treatment with 80 ppm NO and subsequently weaned the iNO concentration if oxygenation improved, which precluded an evaluation of the effects of lower initial iNO doses. These studies did not evaluate individual doses systematically in a method that could be interpreted. However, a recent randomized, controlled, dose-response

*Pediatric Heart Lung Center and the Section of Neonatology, Department of Pediatrics, The University of Colorado School of Medicine and The Children’s Hospital, Denver, CO.
trial in term newborns who had hypoxemic respiratory failure evaluated the effects of sustained exposure to different doses of iNO in different treatment groups. Patients were randomized to treatment with either 0 (placebo), 5, 20, or 80 ppm NO. Each iNO dose improved oxygenation compared with placebo, but there was no difference in responses among treatment groups. However, at 80 ppm, methemoglobinemia (>7%) occurred in 13 of 37 patients (35%), and high inspired NO\textsubscript{2} concentrations were measured in 7 of 37 patients (19%). Thus, 80 ppm iNO was no more effective in improving oxygenation than 5 or 20 ppm, but it was associated with adverse effects. Unfortunately, this trial was limited by early termination due to slow enrollment and the exclusion of lung recruitment approaches to optimize iNO efficacy.

Available evidence supports the use of doses of iNO beginning at 20 ppm in term newborns who have PPHN. Although brief exposures to higher doses (40 to 80 ppm) appear to be safe, sustained treatment with 80 ppm NO increases the risk of methemoglobinemia. The lowest effective initial dose for iNO in term newborns who have PPHN has not been determined, but sustained improvement in oxygenation (after >4 h of treatment) has been demonstrated for doses of less than 10 ppm.

**USE OF ECMO**

Overall, clinical trials of iNO in term newborns have demonstrated an approximately 40% reduction in the use of ECMO. However, not all treated patients experience a sustained improvement in oxygenation; some still require treatment with ECMO. With impending regulatory approval, this raises an important concern about the use of iNO in centers that do not employ ECMO.

Published reports on the use of iNO in ECMO centers have not substantiated early concerns that iNO would affect outcome adversely by delaying use of ECMO. In one study, the median time from randomization to treatment with ECMO was 4.4 and 6.7 hours for the control and iNO groups, respectively. Although this difference was statistically significant, there were no apparent adverse consequences caused by the delay. Patients treated with iNO did not have longer ECMO courses, increased rates of intracranial hemorrhage, or other bleeding complications compared with the control group. Indeed, iNO treatment may play an important role in stabilizing patients before ECMO is initiated. iNO may attenuate pulmonary vasodilatory even without marked increases in PaO\textsubscript{2}, thus improving the chances that ECMO cannulation may proceed without progressive clinical deterioration.

The potential dissemination of iNO therapy to non-ECMO centers, however, warrants a cautious approach. Whether the use of iNO for PPHN in non-ECMO centers will cause undue delays in initiation of transport to an ECMO center, increase the risks of transport, or significantly delay ECMO cannot be determined from the currently available evidence. It is likely that promising new therapies for severe hypoxemic respiratory failure will not be limited to centers that provide all modes of rescue treatment. Although marked improvement in oxygenation occurs in many term newborns who have severe PPHN, sustained improvement may be compromised in some patients by the nature of the underlying disease that leads to progressive atelectasis or systemic hemodynamic disturbances caused by overwhelming sepsis. When the clinical course is complicated by progression in the severity of the cardiopulmonary disease, withdrawal of NO during transport to an ECMO center may lead to acute deterioration. In such cases, iNO may provide an important therapeutic bridge to assure stability during transport. When progressive deterioration in oxygenation occurs during iNO treatment in institutions that cannot offer more advanced rescue therapy, provisions must be in place to transport the patient to the ECMO center without interrupting iNO treatment.

**iNO in Preterm Newborns**

**ENDOGENOUS NO**

Another area of investigation that is of vital clinical importance is iNO therapy in preterm newborns who have hypoxemic respiratory failure. The role of endogenous NO production in vasoregulation of the preterm pulmonary circulation and the effects of iNO in the preterm newborn have received less attention than in the term infant. In the late-gestation ovine fetus, endogenous NO modulates basal pulmonary vascular tone and contributes to the normal fall in pulmonary vascular resistance (PVR) at birth. In addition, iNO causes potent, selective, and sustained pulmonary vasodilation in the normal term newborn lamb. In the preterm lamb at 78% of term (115 d gestation or about 31 wk of human gestational age), inhibition of endogenous NO production increases fetal PVR. Further, when endogenous NO production is blocked during delivery of the preterm lamb, the normal increase in pulmonary blood flow associated with mechanical ventilation and lung inflation is attenuated markedly.

The preterm lamb is an excellent model of respiratory distress syndrome and has been studied extensively. Survival with exogenous surfactant treatment and mechanical ventilation at delivery varies, depending on the gestational age of the lamb and the type of surfactant administered. In very immature lambs (78% of term gestation), gas exchange worsens and PVR increases during mechanical ventilation beyond 60 to 90 minutes after birth, despite treatment with exogenous surfactant at delivery. Intermittent mandatory ventilation over 2 hours in the extremely preterm sheep fetus (115 d gestation, 78% of term) causes progressive worsening of gas exchange and increased PVR. After 2 hours of ventilation, brief NO treatment lowers PVR and improves gas exchange. Moreover, early and continuous treatment with iNO (20 ppm) causes sustained improvement in gas exchange and pulmonary hemodynamics over 3 hours of mechanical ventilation. Lung recruitment strategies employ-
ing high-frequency oscillatory ventilation have been shown to augment the response to low-dose iNO in preterm lambs that have hyaline membrane disease, emphasizing the critical role of adequate lung inflation during inhalational vasodilator therapy.

In addition to its effects on pulmonary hemodynamics and gas exchange during inhalation, endogenous NO may regulate vascular permeability and neutrophil adhesion in the microcirculation. Moreover, in preterm lambs delivered at 78% of term, low-dose iNO (5 ppm) increases pulmonary blood flow and improves gas exchange without increasing pulmonary edema and decreases accumulation of lung neutrophils. In another recent study, lambs delivered at 130 days (90% of gestation) and mechanically ventilated for 5 hours with 20 ppm iNO showed no evidence of lung oxidative stress injury (lung malondialdehyde, reduced glutathione, glutathione reductase) compared with controls.

**iNO THERAPY IN HUMANS**

Preliminary studies in human preterm neonates who have severe hypoxemic respiratory failure support the potential role of low-dose iNO as adjuvant therapy. Low-dose inhaled NO markedly improved oxygenation in a preterm neonate who had group B streptococcal sepsis and severe pulmonary hypertension, allowing reduction in ventilator pressure and inspired oxygen concentration and complete clinical recovery. Preterm neonates who had severe hypoxemia associated with prolonged oligohydramnios and suspected pulmonary hypoplasia showed marked improvement in response to iNO therapy. Five patients survived in this trial, three of whom had severe intracranial hemorrhage (ICH). Another dose–response study in preterm infants concluded that 5 ppm of iNO was as effective as 20 ppm in improving oxygenation. In a small, unmasked, randomized trial of iNO (20 ppm) and dexamethasone treatment, no differences were documented in survival or incidence of chronic lung disease (CLD) or ICH between iNO-treated infants and controls. In yet another dose–response study of iNO in 11 preterm newborns, 5 ppm was shown to be as effective as 20 ppm. Seven (64%) of these infants had ICH, and 5 (45%) had ICH of grade 3 to 4. However, when these results were compared with the NICHD Neonatal Network database (for historical controls matched for severity of illness), the incidence of ICH in preterm newborns not treated with iNO was identical (64%). These observations illustrate the limitations of determining toxicity without appropriately designed clinical trials.

**SAFETY AND EFFICACY**

To begin to address the potential safety and efficacy of iNO in preterm newborns, we recently conducted a randomized controlled trial of iNO in preterm neonates who had severe hypoxemic respiratory failure. We hypothesized that low-dose iNO (5 ppm) would improve survival in affected preterm newborns who were unresponsive to conventional therapies, including surfactant, and would not increase the incidence or severity of ICH or CLD. We randomized 80 preterm newborns (gestational ages <34 wk) who had severe hypoxemic respiratory failure in 12 perinatal centers that provide tertiary care. Forty-eight patients were treated with iNO and 32 served as controls. Treatment assignment was masked. The primary outcome variable was survival to discharge. Secondary outcome variables included incidence and severity of ICH and pulmonary hemorrhage, duration of mechanical ventilation, and incidence of CLD at 36 weeks’ postconceptional age. The groups did not differ in baseline characteristics or severity of disease (\(P_{\text{NO}}/\text{FiO}_2 = 42\pm18 \text{ mm Hg}\) for iNO; 42±16 mm Hg for control; \(P=\text{NS}\)). iNO improved oxygenation acutely after 60 minutes of treatment (\(P_{\text{NO}}/\text{FiO}_2 = 88\pm12 \text{ mm Hg}\) for iNO; 56±9 mm Hg for control; \(P<0.05\)). Survival to discharge was 52% in the iNO group and 47% in controls (\(P=\text{NS}\)). Causes of death were related primarily to extreme prematurity and were similar between groups. Total ventilator days for survivors was less for the iNO group (\(P=0.046\)). In contrast to uncontrolled pilot studies, there was no difference in the incidence of ICH between the control and iNO-treated groups (Figure).

Thus, low-dose iNO resulted in acute improvement in oxygenation in preterm newborns who had severe hypoxemic respiratory failure without increasing the risk of bleeding complications, including ICH. Low-dose iNO may be effective as a lung-specific anti-inflammatory therapy to diminish lung neutrophil accumulation and the attendant inflammatory injury that contributes to the evolution of CLD. Sufficient evidence now may be available to warrant a controlled trial of low-dose iNO in preterm newborns who have less severe disease.

**Summary**

iNO improves oxygenation and decreases use of ECMO in term newborns who have PPHN. From the available information, a reasonable recommendation for the initial dose of iNO in the term infant is 20 ppm, with the dose reduced over time. Toxicity is apparent at 80 ppm, causing increases in methemoglobinemia and inspired NO\(_2\). High doses (>20 ppm) of iNO also may prolong bleeding time, but clinically significant increases in bleeding complications have not been reported in term newborns. Finally, there is increasing evidence for the potential role of low-dose iNO (5 ppm) in preterm newborns who
have hypoxemic respiratory failure. This therapy causes acute improvement in oxygenation and may prove to be useful as a lung-specific anti-inflammatory treatment. However, clinical application currently should be limited to controlled trials that target outcomes of both safety and efficacy.

SUGGESTED READING
Subhadar NV, Ryan SW, Shaw NJ. Open randomised controlled trial of inhaled nitric oxide and early dexamethasone in high risk preterm infants. Arch Dis Child. 1997;77:F185–F190
Clinical Trials of Inhaled Nitric Oxide Therapy in the Newborn
John P. Kinsella
Pediatrics in Review 1999;20:e110
DOI: 10.1542/pir.20-11-e110

Updated Information & Services
including high resolution figures, can be found at:
http://pedsinreview.aappublications.org/content/20/11/e110

References
This article cites 24 articles, 8 of which you can access for free at:
http://pedsinreview.aappublications.org/content/20/11/e110#BIBL

Permissions & Licensing
Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at:
http://classic.pedsinreview.aappublications.org/site/misc/Permissions.xhtml

Reprints
Information about ordering reprints can be found online:
http://classic.pedsinreview.aappublications.org/site/misc/reprints.xhtml
Clinical Trials of Inhaled Nitric Oxide Therapy in the Newborn
John P. Kinsella

Pediatrics in Review 1999;20:e110
DOI: 10.1542/pir.20-11-e110

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://pedsinreview.aappublications.org/content/20/11/e110