



Recommendations for the Use of Inhaled Nitric Oxide Therapy in Premature Newborns with Severe Pulmonary Hypertension

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Nitric oxide is a potent endothelium-derived factor that has diverse effects on the pulmonary circulation, including vasodilation, pro-angiogenic, anti-inflammatory, and anti-oxidant properties.¹ Following extensive preclinical and promising pilot studies, inhaled nitric oxide (iNO) therapy was extensively studied in multicenter randomized trials in term infants with severe hypoxemia associated with pulmonary hypertension (PH).² These studies consistently demonstrated striking improvement in oxygenation and reduction in the need for extracorporeal membrane oxygenation (ECMO) therapy, which led to the approval by the Food and Drug Administration of iNO therapy for use in newborns >34 weeks gestation with hypoxemic respiratory failure and persistent PH of the newborn (PPHN). Since approval, iNO use has led to sustained reduction in ECMO utilization with no serious adverse effects identified with long-term follow-up.

iNO for the Prevention of Bronchopulmonary Dysplasia

iNO is uniquely suited to the treatment of PPHN due to its selectivity for the pulmonary circulation, the absence of toxicities when used at low doses, and its demonstrated efficacy in decreasing the need for treatment with extracorporeal life support.^{3,4} The effectiveness of iNO in the near-term and term newborn is largely due to its properties as a selective pulmonary vasodilator; however, numerous laboratory studies also demonstrated other important effects, such as decreasing lung inflammation,⁵ reducing oxidant stress,⁶ and enhancing alveolarization and lung growth.⁷⁻⁹ These observations formed the basis for studying iNO in premature newborns at risk for developing bronchopulmonary dysplasia (BPD), with at least 16 randomized, controlled trials completed over the last 2 decades. Despite promising findings in some studies showing a reduction in BPD in subsets of

premature newborns,^{10,11} subsequent trials did not confirm the benefits.^{12,13} In fact, meta-analyses of these studies reported no net improvement in either chronic lung disease or developmental sequelae.¹⁴ In addition, an individual-patient data meta-analysis of 3298 premature newborns enrolled in 12 randomized, controlled trials designed to study the effects of iNO on BPD prevention showed that treatment with iNO did not reduce the incidence of BPD. Importantly, iNO therapy also was not associated with an increased risk of adverse events. This and other prior meta-analyses led to the conclusion by an National Institutes of Health Consensus Development Conference¹⁵ and, more recently, the American Academy of Pediatrics (AAP) Committee on the Fetus and Newborn¹⁶ that the use of iNO to prevent BPD is not supported by available evidence.

iNO for the Treatment of Severe PH in the Preterm Infant

Although the focus of the prior randomized, controlled trials was to test the role of iNO in BPD prevention, the potential role for iNO in preterm infants for the acute management of severe hypoxemic respiratory failure has not been fully addressed. In particular, there is a subset of premature newborns with severe PPHN for which iNO may likely be a

AAP	American Academy of Pediatrics
BPD	Bronchopulmonary dysplasia
ECMO	Extracorporeal membrane oxygenation
iNO	Inhaled nitric oxide
PH	Pulmonary hypertension
PPHN	Persistent pulmonary hypertension of the newborn
PPROM	Preterm premature rupture of membranes
RCT	Randomized control trial

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safe and effective therapy. PPHN in premature newborns (associated with prolonged oligohydramnios, pulmonary hypoplasia, and other causes) is pathophysiologically similar to the syndrome in term infants. Individual case reports and case series suggest that the response to iNO in premature newborns with PPHN is similar to near-term and term newborns enrolled in the 2 pivotal trials that led to Food and Drug Administration approval for infants >34 weeks gestation.^{3,4} The earliest report of iNO treatment in a premature newborn with PPHN described marked reduction in extrapulmonary right to left shunting and oxygenation in a 28 weeks gestation infant with Group B Streptococcal sepsis.¹⁷ Several case series described responses of premature newborns with PPHN associated with prolonged oligohydramnios and suspected pulmonary hypoplasia, typically associated with high mortality. Peliowski reported 8 premature newborns of 24–31 weeks gestation with severe PPHN associated with prolonged rupture of membranes and suspected pulmonary hypoplasia.¹⁸ All infants had improvement in PH and oxygenation, and 6 infants survived. Chock et al reported on a subset of 12 premature newborns enrolled in the Preemie Inhaled Nitric Oxide (PiNO) Trial with pulmonary hypoplasia after preterm premature rupture of membranes (PPROM).¹⁹ Six infants were treated with iNO with a mortality rate of 33% compared with 67% mortality for the 6 infants in the placebo control group. Shah and Kluckow described outcomes for infants following PPRM, and reported that survival improved from 62% to 90% after the introduction of iNO and high frequency oscillatory ventilation in the management.²⁰ More recently, Semberova et al published a series of 22 premature infants with a history of PPRM, pulmonary hypoplasia, and PPHN who were treated with iNO with a survival rate of 86%.²¹ Common to all of these reports is severe hypoxemic respiratory failure and PPHN presenting in the first day of life that had marked improvement in oxygenation after treatment with iNO, similar to the response typical for the term newborn with idiopathic PPHN.

Controversies

Although the use of iNO in premature infants with PPHN was not addressed in the AAP Statement, the National Institutes of Health Consensus Statement concluded that “there are rare clinical situations, including PH or hypoplasia, that have been inadequately studied in which iNO may have benefit in infants <34 weeks gestation” and that “use in this population should be left to clinical discretion.” Unfortunately, a proper randomized control trial (RCT) of iNO in premature newborns with severe PPHN physiology causing critical hypoxemia due to extrapulmonary right-to-left shunting has not been done. However, conducting a RCT today is not feasible for a number of reasons. Severe early PPHN occurs rarely, in less than 2% of all preterm births; therefore, any RCT would require an exceptionally large network of clinical sites. There is also a lack of equipoise about the safety and efficacy of iNO with some clinicians re-

stricting iNO use to infants >34 weeks gestation and others selectively treating premature infants with iNO who have life-threatening hypoxemia due to PPHN physiology during the first days after birth. Moreover, unlike the trials in term newborns where ECMO was available for rescue therapy, for a RCT in premature newborns the outcome measure would be mortality because ECMO is not a clinical option for this population. This would not allow for an acceptable study design for clinicians who recognize that iNO is a potent and selective pulmonary vasodilator for the treatment of PPHN with a very favorable safety profile.

In the absence of compelling RCT results for premature newborns with PPHN, and likely related to the recent AAP Statement, there are concerning anecdotal reports that third party payers are increasingly denying payment for any use of iNO in the premature newborn, and in some cases are even denying payment for other hospital charges associated with iNO use. There are also worrying reports that some hospitals have asked neonatologists to reduce or eliminate the use of iNO in any newborn <34 weeks gestation, regardless of the etiology of the hypoxemic respiratory failure. These developments have led some centers to withhold treatment with iNO even in premature infants with life-threatening hypoxemia caused by PPHN, or to use other therapies for which there is little or no evidence for safety and efficacy in this population. Over 2 decades, more than 4600 premature newborns have been enrolled in 16 RCTs yielding safety data on acute effects and long-term outcomes. The safety profile is well established and iNO should be the pulmonary vasodilator of choice in premature newborns with severe PPHN, particularly in association with prolonged oligohydramnios and pulmonary hypoplasia.

It is unlikely that a proper RCT to test the role of iNO therapy in this population could be conducted, and retrospective registries do not provide enough detail to be informative. Therefore, we propose a prospective registry to identify premature newborns with severe PH who (based upon local practice) are treated with iNO, another pulmonary vasodilator, or no specific PH therapy. Although not an RCT, the results of this registry would help define current practice and provide outcome comparisons that would inform the debate about the role of iNO for PPHN in the premature newborn.

Recommendations

Based on the above observations, the Pediatric Pulmonary Hypertension Network proposes the following recommendations for the role of iNO in premature newborns:

- (1) iNO therapy should not be used in premature infants for the prevention of BPD, as multicenter studies data have failed to consistently demonstrate efficacy for this purpose;
- (2) iNO therapy can be beneficial for preterm infants with severe hypoxemia that is primarily due to PPHN physiology rather than parenchymal lung

disease, particularly if associated with prolonged rupture of membranes and oligohydramnios;

- (3) 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 randomized clinical trials for BPD prevention; and
- (4) Placebo controlled trials are not feasible in the target population; therefore, alternate study designs such as the development of multicenter registries, informatics strategies, and other approaches should be used to address issues regarding the efficacy and safety of therapeutic options for preterm infants with life threatening PPHN physiology.

We conclude that iNO therapy has successfully improved clinical management and has lowered the need for ECMO therapy in term and near-term infants, but more studies are needed to more precisely define its role in premature neonates. Although we recommend that iNO not be routinely used for the prevention of BPD, we believe that iNO therapy may have an important role for subgroups of preterm infants with severe PH, especially in the setting of PPHN physiology associated with oligohydramnios, lung hypoplasia, and sepsis. Owing to promising case series findings, extensive safety data in preterm infants from past metaRegister of Controlled Trials and the lack of safety or efficacy data concerning other targeted PH therapies (PH-specific drugs), we believe that it is reasonable to use iNO in this subgroup of critically ill preterm infants. We encourage ongoing research for the impact of iNO and other therapies in the setting of severe PH in preterm infants. ■

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