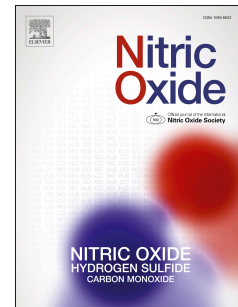


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## **Inhaled Nitric Oxide Use in Neonates: Balancing What is Evidence-Based and What is Physiologically Sound**

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LS, CJW, CD drafted the manuscript; LS, CJW, CD and JK edited and revised manuscript.

**Key Words:** Nitric oxide; persistent pulmonary hypertension of the newborn; pulmonary arterial hypertension; neonate; respiratory failure; bronchopulmonary dysplasia

*Abbreviations:* bronchopulmonary dysplasia (BPD), hypoxemic respiratory failure (HRF), iNO (inhaled nitric oxide), intraventricular hemorrhage (IVH), oxygenation index (OI), mechanical ventilation (MV), randomized control trials (RCTs), partial pressure of oxygen (PaO<sub>2</sub>), persistent pulmonary hypertension of the newborn (PPHN), pulmonary hypertension (PH), pulmonary arterial hypertension (PAH), low birth weight (VLBW)

## **I. Abstract**

Inhaled nitric oxide is a powerful therapeutic used in neonatology. Its use is evidenced-based for term and near-term infants with persistent pulmonary hypertension; however, it is frequently used off-label both in term and preterm babies. This article reviews the off-label uses of iNO in infants. Rationale is discussed for a selective application of iNO based on physiologically guided principles, and new research avenues are considered.

## **II. Review of nitric oxide and on-label use of iNO in neonates**

Nitric oxide (NO) is an endogenous signaling molecule with a number of important biologic effects. One of the major roles of NO in the developing lung is regulation of pulmonary vascular tone. Key studies in the ovine model of persistent pulmonary hypertension of the newborn (PPHN) revealed that inhalation of NO (iNO) causes potent and selective pulmonary vasodilation [1]. Shortly thereafter the first reports of the use in neonates with PPHN demonstrated that iNO was associated with improvement of oxygenation with no detectable toxicity [2; 3]. Numerous RCTs followed, demonstrating that iNO improves oxygenation and decreases the need for ECMO in term and near-term neonates with PPHN [4; 5; 6; 7; 8; 9; 10; 11; 12]. These studies led to FDA approval for the use of iNO as a pulmonary vasodilator in term and near-term (>34 weeks' gestation) neonates with hypoxic respiratory failure associated with clinical or echocardiographic evidence of pulmonary hypertension. With the establishment of iNO safety and efficacy in neonates with PPHN its use in additional neonatal diseases associated with pulmonary hypertension was explored. The purpose of this review is to highlight the evidence and current practices of the off-label use of iNO in neonates.

## **III. Off label use of iNO in infants with pulmonary hypertension associated with CDH & BPD**

While the majority of neonates treated with iNO have transient pulmonary hypertension (PH) secondary to PPHN, an increasing number of infants with PH secondary to developmental lung diseases such as congenital diaphragmatic hernia (CDH) and bronchopulmonary dysplasia (BPD) receive iNO (Ref).

*Congenital Diaphragmatic Hernia:*

CDH is a congenital malformation associated with high mortality and morbidity and severity of PH predicts outcome in this population of infants [13; 14; 15; 16]. While RCTs have not demonstrated an effect on mortality or ECMO utilization with iNO use in this select population the use of iNO in neonates with CDH is widespread [5; 17; 18; 19]. Hypoxemia in patients with CDH occurs secondary to both intrapulmonary shunting due to lung hypoplasia and elevation of pulmonary vascular resistance leading to extrapulmonary shunting of deoxygenated blood across the foramen ovale and patent ductus arteriosus into the systemic circulation [14]. As the physiology of this heterogeneous population of infants is complex, interpretation of each patient's unique physiology is critical to determining whether a patient may benefit from use of a potent pulmonary vasodilator such as NO. One of the key factors impacting the response of patients with CDH to pulmonary vasodilators such as iNO is the presence and degree of left ventricular dysfunction. In the setting of left ventricular dysfunction and consequent pulmonary venous hypertension the use of pulmonary vasodilators may be detrimental and lead to development of pulmonary hemorrhage [20]. The use of echocardiography in this population to guide management is essential. Reports on improved oxygenation with the combination of milrinone and iNO in infants with CDH provide support for this strategy [21]. While RCTs have not demonstrated an effect of iNO on mortality or ECMO utilization in the acute setting, PH can occur at any point in the course of an infant with CDH. iNO is associated with improvement in oxygenation in those infants who develop post-operative PH [22]. Overall the treatment strategy for patients with CDH should be tailored to each individual patient and their physiology and is too complex for this review. The reader is referred to a detailed review and expert recommendations on the use of iNO in neonates with CDH by Gien & Kinsella [23].

### *Bronchopulmonary Dysplasia:*

Prospective studies show that PH develops in 14-18% of preterm infants with the chronic lung disease of prematurity, bronchopulmonary dysplasia (BPD) and contributes significantly to clinical outcomes [24; 25]. Multiple pre-clinical models have demonstrated impaired NO signaling in BPD and NO administration to rodents with BPD prevents PH, improves alveolarization and has anti-inflammatory effects [26; 27; 28; 29]. While pre-clinical evidence provides support for the use of iNO in patients with PH associated with BPD there are no RCTs evaluating the effectiveness of vasodilator therapies including iNO to treat PH in infants with BPD. Treatment of PH in these infants is based upon expert opinion and includes the optimization of gas exchange and a thorough evaluation of PH etiology including consideration of cardiac catheterization [30; 31; 32; 33]. It is increasingly recognized that these infants may have underlying LV dysfunction, intracardiac or extracardiac shunts, PV stenosis, or PVOD contributing to PH and initiation of a pulmonary vasodilator in these patients would be deleterious [34; 35]. Literature on the use of iNO in this population is limited to reports in select patients with BPD, many of whom did not have demonstrable evidence of PH but did have an acute improvement in oxygenation [36; 37; 38]. If iNO is used in infants with established BPD and PH, given its rapid onset and issues with cost and feasibility of delivery, iNO is used primarily to treat acute PH episodes. If PH persists despite optimization of ventilation, following a thorough evaluation of PH etiology select infants may benefit from prolonged iNO as treatment with oral pulmonary vasodilators is initiated.

#### **IV. Use of iNO in preterm infants to prevent BPD**

##### **Preclinical rationale to investigate iNO to prevent bronchopulmonary dysplasia.**

BPD is associated with long-term pulmonary and neurodevelopmental impairment [39]. Despite advances in neonatal care, BPD is not decreasing, and incidence may be increasing in the most immature babies [40]. Preclinical data provided rationale to evaluate iNO as a potential therapeutic for the prevention of BPD. In a variety of pre-clinical models, iNO improves oxygenation and pulmonary vascular resistance, decreases pulmonary oxidative stress and inflammation, and improves alveolar development [26; 41; 42; 43; 44]. However, concerns exist for unintended side effects in the most vulnerable early gestational ages. iNO increases bleeding time in adults and impairs platelet aggregation in neonates, thus potentially could increase intraventricular hemorrhage (IVH) [45; 46]. Additionally, the antioxidant defense system is underdeveloped in premature infants, and iNO could induce an oxidative burden by rapidly interacting with superoxide anion, creating the highly toxic prooxidant, peroxynitrite [47]. Trials in human neonates were designed to evaluate these potential benefits as well as harms.

#### **Clinical Trials in premature infants do not support use of iNO for the prevention of BPD.**

Multiple randomized controlled trials (RCTs) have investigated short and long-term outcomes after iNO therapy in premature infants. These studies vary significantly in the age and illness severity at randomization, maximum dose and duration of iNO prescribed, and policies defining iNO response and weaning. Perhaps not surprising in light of this heterogeneity, the results of these trials are inconsistent. Overall, they do not support the use of iNO to prevent BPD. The studies can be categorized by those evaluating *early use* (initiated < 3 days, either for routine prophylaxis or “rescue” of hypoxemic respiratory failure) and *later/selective use* (started > 4 days of life, targeting infants at higher risk for BPD).

#### **Early iNO for the prevention of BPD**

Several RCTs conducted in the USA, Canada and Europe tested the early use of iNO, initiated prior to 3 days of life in infants who were mechanically ventilated [48; 49; 50; 51; 52]. An initial single center trial demonstrated promising results with a reduction in death or bronchopulmonary dysplasia [52]. However, the majority of the subsequent multicenter trials did not corroborate these findings [48; 49; 50;

51]. Subgroup analysis in some of these studies suggested a potential benefit in the larger VLBW infants. Schreiber et al demonstrated improved outcomes for infants >1000g [52] and Kinsella et al showed significant reductions in death or BPD in neonates 1000-1250g [49].

Noninvasive ventilation is increasingly used in the VLBW population, as a result of evidence that avoiding mechanical ventilation prevents BPD [53]. Kinsella et al tested if early noninvasive iNO initiated <3 days would prevent subsequent intubation or BPD in infants <1250. They found no difference in the number of babies requiring mechanical ventilation or developing BPD [54].

#### **Late iNO for the prevention of BPD**

Two large multicenter trials evaluated a selective approach for iNO, by randomizing infants with a continued requirement for mechanical ventilation (MV) after 5-7 days, thus considered higher risk for BPD. There is less heterogeneity between these two trials, with relative similarities in recruited patient population, doses of inhaled nitric oxide, and specified outcome measures. Despite this, their results are inconsistent. In the NO CLD trial, 588 infants still intubated between 7-21 days were randomized to iNO or placebo for up to 21 days or placebo. Those treated with iNO exhibited a significant decrease in the incidence of survival without BPD [55]. In contrast, the NEWNO trial evaluated 451 infants reliant on MV between 5-14 days. In this study, iNO demonstrated no improvement in mortality, BPD, or other short- or long-term outcomes [56].

Multiple meta-analyses and systematic reviews have addressed the combined results of these trials. In 2011, the National Institute of Health (NIH) statement, the Johns Hopkin University Evidence-Based Practice Center, and the meta-analysis of individual patient data from 12 of these trials concluded iNO demonstrated no significant improvements in short-term or long-term outcomes in preterm infants [57; 58; 59]. In 2014, American Academy of Pediatrics (AAP) guidelines recommended against the *routine* use of iNO in premature babies, citing cost and insufficient evidence for benefit [60]. A recent systematic review in 2017 affirmed these findings, concluding that that iNO does not prevent BPD or improve survival in premature neonates [57; 61; 62].

#### **V. Why does use of iNO continue in the VLBW population?**

Despite these recommendations, use of iNO in premature infants continued and even increased in some institutions [63]. There are several plausible explanations for why the utilization of iNO has increased despite multiple studies revealing no overall significant benefit in VLBW babies. VLBW infants experience hypoxemic respiratory failure primarily as a result of V/Q mismatch and intrapulmonary shunting as a result of surfactant deficiency. The contribution of PPHN to hypoxemia in this population is increasingly recognized. Inhaled nitric oxide has demonstrated ability to transiently improve oxygenation in this population, measured by partial pressure of oxygen (PaO<sub>2</sub>) and oxygenation index (OI) [64; 65]. None of the randomized controlled trials conducted in this population evaluated PPHN defined by echocardiogram, thus it can be reasonably argued until rigorously studied, a therapeutic challenge may be considered. In the setting of a profoundly hypoxemic premature infant with lack of safe alternative therapeutic options, clinical decision making is often guided on prior experience, physiologic rationale and biologic plausibility.

This rationale guides *selective* application of iNO to individual patients based on physiologic principles [66; 67]. The NIH statement and the American Thoracic Society and Pediatric PH guidelines support considering this individualized approach in specific subsets of premature patients [58; 68; 69]. Preterm infants with severe hypoxemia secondary to PPHN physiology, as well as those with pulmonary hypoplasia, prolonged rupture of membranes and oligohydramnios are advocated as groups to consider a trial of treatment. It is likely that recruiting enough patients in a multicenter randomized trial powered to detect meaningful outcomes is impractical given the lack of equipoise among clinicians when dealing with these critically ill babies. However, prospective data collection through the establishment of patient registries represents one option to learn more about the role of iNO in the treatment of these illnesses.

## **VI. Is there any evidence to support off-label use of iNO in subgroups of preterm infants?**

*Do VLBW infants with pulmonary hypoplasia and/or PPHN benefit from iNO?*

Preterm infants with pulmonary hypoplasia may have increased pulmonary vascular reactivity due to impaired angiogenesis. Several smaller case series suggested babies who experienced



oligohydramnios or PROM in utero respond to iNO [70; 71]. Two recent publications retrospectively evaluated a larger number of infants and are less clear regarding benefit in these groups. Chandrasekharan et al reported a single center study comparing age-matched controls to infants treated with iNO [72]. Surviving infants treated with iNO were more frequently exposed to preterm prolonged rupture of membrane (PPROM) when compared to non-survivors. However, Ellsworth et al evaluated iNO in a multicenter cohort study of preterm neonates with a clinical diagnosis of pulmonary hypoplasia [73]. They used a sample of 90,000 infants, of which 0.8% had a diagnosis of pulmonary hypoplasia and were included in the study. They found no statistically significant improvement in mortality, BPD, PVL or ROP in infants with pulmonary hypoplasia treated with iNO. However, these infants were identified by provider discretion, thus without established set criteria or diagnostic precision.

None of the prospective multicenter trials of iNO in premature babies required pre-randomization echocardiograms. This prohibited subgroup analysis of infants with true PPHN physiology. In Ellsworth et al, subgroup analysis compared infants with pulmonary hypoplasia *with* PPHN to infants with pulmonary hypoplasia *without* PPHN. PPHN was determined by provider discretion. They found a 33% reduced risk of in-hospital mortality (HR 0.67; 95% CI 0.45-1.01), in infants with pulmonary hypoplasia and PPHN treated with iNO [73]. Prospective study of this population is needed.

*Is there a race-specific treatment effect of iNO in the preterm infant population?*

Following the publication of multiple randomized controlled trials evaluating the use of iNO in premature infants, subsequent systematic reviews and individual patient data (IPD) meta-analysis, the NIH Consensus Development Conference concluded that “taken as a whole, the available evidence does not support use of iNO in early-routine, early-rescue, or later-rescue regimens in the care of premature infants.”[58] However, the group acknowledged that ***subgroup analysis were hypothesis generating, and could serve as the basis for recommending future research directions.*** In particular, the commissioned

systematic review from The Johns Hopkins University Evidence-based Practice Center stated “there is insufficient evidence to evaluate the relationship between iNO therapy and infant sex, race/ethnic group, gestational age, or socioeconomic status”[74]. However, the MAPPiNO IPD meta-analysis showed a non-significant trend toward greater treatment effect in non-white infants [59].

Recently, Askie and colleagues have published “Race Effects of Inhaled Nitric Oxide in Preterm Infants: An Individual Participant Data Meta-Analysis” (RiNOP) [75]. The analysis was limited to three trials: the Schreiber trial [52], NOCLD [55], and the NEWNO trial [56]. The rate of death or BPD with iNO treatment in African American infants was 49%, compared to 63% in controls (RR .77; 95% CI, 0.65-0.91) and the authors concluded that “iNO therapy should be considered for preterm African American infants at high risk for BPD. iNO to prevent BPD in African Americans may represent an example of racially customized therapy for infants” [75].

Prior to concluding that “iNO in African Americans may represent an example of a racially customized therapy for infants,” we must acknowledge the limitation of making this conclusion based on sub-group analysis. These studies were not designed to determine the relationship between race/ethnicity and response to iNO. Infant race was determined by maternal self-report; paternal race/ethnicity was not considered. Prospective studies on the relationship between race/ethnicity and a response to therapy should have thorough descriptions of how race/ethnicity were determined and be adequately powered to interrogate this relationship across multiple groups. Of note, RiNOP found clinically significant treatment effects in other racial/ethnic groups evaluated (10% in Hispanic), although limited numbers of subjects may have precluded this finding reaching clinical significance. Furthermore, the authors of RiNOP have used maternal self-reported race/ethnicity as a proxy for the infants genetics, citing “a high concordance between genetic African ancestry and self-reported African American race [75]. However, there are significant limitations of using race as a proxy for genetic makeup [76; 77]. Race is a sociologic variable and travels with a diverse set of exposures and environments. The impact of these variables on the observed treatment effect was not considered. Without a thorough understanding of the interplay of race/ethnicity and these other exposures, we risk therapeutic misuse of iNO in the preterm population[78].

Thus, while the findings of RiNOP are hypothesis-generating, further prospective, randomized clinical trials are necessary to evaluate the observed treatment effect [79].

## VII. Conclusion

Inhaled nitric oxide is a powerful and useful therapeutic, proven effective in term and near-term neonates with PPHN. The off-label uses of iNO for infants are primarily based on physiologically guided rationale as opposed to evidence-based medicine. Overall, trials of iNO in VLBW infants have not shown evidence of harm, suggesting it is likely safe. Future trials prospectively randomizing infants with echocardiographic evidence of PPHN, history of oligohydramnios/pulmonary hypoplasia, or by race are needed to further guide clinical care.

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