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CLINICAL REPORT

Use of Inhaled Nitric Oxide in Preterm Infants

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KEY WORDS
inhaled nitric oxide, preterm infants, hypoxic respiratory failure, bronchopulmonary dysplasia

ABBREVIATIONS
BPD—bronchopulmonary dysplasia
iNO—inhaled nitric oxide
NO—nitric oxide
NOCLD—Nitric Oxide Chronic Lung Disease study group

abstract

FREE

Nitric oxide, an important signaling molecule with multiple regulatory effects throughout the body, is an important tool for the treatment of full-term and late-preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure. Several randomized controlled trials have evaluated its role in the management of preterm infants ≤34 weeks' gestational age with varying results. The purpose of this clinical report is to summarize the existing evidence for the use of inhaled nitric oxide in preterm infants and provide guidance regarding its use in this population. *Pediatrics* 2014;133:164–170

INTRODUCTION

Nitric oxide (NO) is an important signaling molecule with multiple regulatory effects throughout the body. In perinatal medicine, inhaled nitric oxide (iNO) was initially studied for its pulmonary vasodilating effects in infants with pulmonary hypertension and has since become an important tool for the treatment of full-term and late-preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure.[1] Inhaled NO also has multiple and complex systemic and pulmonary effects. In animal models of neonatal chronic lung disease, iNO stimulates angiogenesis, augments alveolarization, improves surfactant function, and inhibits proliferation of smooth muscle cells and abnormal elastin deposition.[2–6] Although the evidence for similar benefits in preterm infants is lacking, the off-label use of iNO in this population has escalated.[7] A study published in 2010 reported a sixfold increase (from 0.3% to 1.8%) in the use of iNO among infants born at less than 34 weeks' gestation between 2000 and 2008.[7] The greatest increase occurred among infants who were born at 23 to 26 weeks' gestation (0.8% to 6.6%). The National Institutes of Health convened a consensus panel in October 2010 to evaluate the evidence for safety and efficacy of iNO therapy in preterm infants. After reviewing the published evidence, the panel concluded that the available evidence does not support the use of iNO in early routine, early rescue, or later rescue regimens in the care of infants born at less than 34 weeks' gestation and that hospitals, clinicians, and the pharmaceutical industry should avoid marketing iNO for this group of infants.[8] An individual-patient data meta-analysis of 14 randomized controlled trials reached similar conclusions.[9] The purpose of this clinical report is to summarize the

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existing evidence for the use of iNO in preterm infants and provide guidance regarding its use in this population.

LITERATURE REVIEW

Use of iNO in Preterm Infants With Respiratory Failure

The benefits associated with iNO therapy in full-term and late-preterm infants with persistent pulmonary hypertension of the newborn and hypoxemic respiratory failure initiated interest in exploring whether iNO could reduce the rates of death and neonatal morbidities in more immature infants. Pilot studies reported short-term improvement in oxygenation with iNO, but no significant benefit was observed in mortality or other morbidities.[10–15] Subsequently, several randomized clinical trials were undertaken.[16–23] Table 1 outlines the study population, entry criteria, and dose and duration of iNO treatment and summarizes the outcomes for all published randomized controlled trials. Only 1 small trial of 40 patients reported a beneficial effect on survival (Table 1). Subgroup analyses of secondary outcomes have provided conflicting results. Post hoc analysis of the Neonatal Research Network study suggested that iNO therapy was associated with reduced rates of death and bronchopulmonary dysplasia (BPD) in infants with a birth weight greater than 1000 g, but higher mortality and increased risk of severe intracranial hemorrhage in infants weighing 1000 g or less at birth.[17] In contrast, another large multicenter US trial reported no significant difference in the primary outcome of death or BPD between treated and control groups; however, infants treated with iNO had fewer brain lesions (eg, grade 3 or 4 intracranial hemorrhage, periventricular leukomalacia, and/or ventriculomegaly) noted on cranial ultrasonography.[20] A European multicenter study reported that infants randomized to iNO treatment had longer duration of ventilation, time on oxygen therapy, and length of hospital stay compared with the placebo group, although none of these results were statistically significant.[19]

Use of iNO in Preterm Infants to Improve the Rate of Survival Without BPD

Lung pathology in preterm infants with BPD is characterized by reduced numbers of large alveoli and abnormal pulmonary vasculature development. Surfactant deficiency, ventilator-induced lung injury, oxygen toxicity, and inflammation appear to play important roles in its pathogenesis.[26,27] In animal models of neonatal lung injury, iNO promotes angiogenesis, decreases apoptosis, and reduces lung inflammation and oxidant injury.[28–30] In an early study of iNO use in preterm infants, the incidence of BPD was reduced in treated infants who required ventilator support.[16] Of 3 subsequent large randomized trials designed to evaluate the effect of iNO therapy on survival without BPD,[20,24,25] 2 found no significant benefit[20,25] (Table 1). A third trial, which featured late treatment (7–21 days of age), a longer duration of drug exposure (25 days), and a higher cumulative dose, demonstrated a modest but statistically significant beneficial effect (44% iNO vs 37% placebo; $P = .042$).[24] A subgroup analysis showed that the beneficial effect was seen in infants enrolled between 7 and 14 days of age but not those enrolled between the ages of 15 and 21 days.[24]

EFFECTS OF INO THERAPY ON NEURODEVELOPMENTAL OUTCOME

Studies in animal models suggest that iNO may have direct beneficial effects on the brain through mechanisms involving the cerebral vasculature and/or neuronal maturation.[31,32] Other investigators have described a possible role for intravascular NO-derived molecules in conserving and stabilizing NO bioactivity that may contribute to the regulation of regional blood flow and oxygen delivery.[33,34] Neurodevelopmental outcome has been reported for 6 clinical trials,[35–40] and of these, 1 noted a more favorable neurodevelopmental outcome at 1 year of age among the preterm cohort treated with iNO but no difference in the rate of cerebral palsy.[36]

EFFECTS OF INO THERAPY ON LONG-TERM PULMONARY OUTCOME OF SURVIVORS

In animal models, iNO decreases baseline airway resistance and may increase the rate of alveolarization.[2–6] To date, only 2 studies have reported respiratory outcomes of preterm infants treated with iNO.[41,42] In a telephone survey that included 456 infants in the Nitric Oxide Chronic Lung Disease (NOCLD) study group, the use of bronchodilators, inhaled steroids, systemic steroids, diuretics, and supplemental oxygen during the first year of life was less in the iNO-treated group, but there were no significant differences in the frequency of wheezing or the rate of rehospitalization. In the Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide multicenter trial, follow-up at 1 year of age showed no difference in maximal expiratory flow at functional residual capacity, wheezing, readmission rate, or use of respiratory medications.[42]

RESULTS OF META-ANALYSES OF STUDIES EVALUATING THE USE OF INO IN PRETERM INFANTS

Two published meta-analyses found no overall significant effect of iNO on the rate of mortality, BPD, intraventricular hemorrhage, or neurodevelopmental impairment.[43,44] In view of the limitations

TABLE 1 Randomized Controlled Trials of iNO in Preterm Infants

Author, Year	*n*	Gestational Age, wk	Birth Weight, g	Age at Enrollment	Entry Criteria	iNO Protocol	Primary Outcome	Study Results
Subhedar, 1997[11]	42	<32	—	96 h	Need for mechanical ventilation and high risk of developing CLD	20 ppm for at least first 2 h and then 5 ppm for 3–4 d	Death and/or CLD before discharge	No difference in primary outcome
Kinsella, 1999[12]	80	≤34	—	≤7 d	aAO_2 ratio <0.1 on 2 consecutive blood gases in first 7 d of life	5 ppm for 7–14 d	Survival	No difference in primary outcome; no difference in rate of IVH or CLD
The French-Belgian iNO Trial, 1999[13]	85	<33	—	<7 d	OI between 12.5 and 30.0 on 2 consecutive blood gases at least 1 h apart	10–20 ppm for a minimum of 2 h	OI reduction of ≥33% or at least 10 points	More treated infants achieved primary outcome; no difference in median OI at 2 h; no difference in survival or other outcomes
Srisuparp, 2002[15]	34	—	<2000	<72 h	OI ranging from >4 to >12 based on birth wt	20 ppm for 24–48 h and then 5 ppm for maximum of 7 d	Change in oxygenation	Improved oxygenation with treatment but no difference in survival or IVH
Schreiber, 2003[16]	207	<34	<2000	<72 h	Need for mechanical ventilation	10 ppm for first day then 5 ppm for 6 d	Death and survival without BPD at 36 wk postmenstrual age	Treatment associated with a decrease in the combined incidence of BPD and death; no difference in mortality alone
Van Meurs, 2005[17]	420	<34	401–1500	4–120 h; mean 26–28 h	OI ≥10 on 2 consecutive blood gases between 30 min and 12 h apart	5–10 ppm for maximum of 14 d	Incidence of death or BPD	No difference in primary outcome; no difference in rate of BPD, severe IVH, or PVL. Post hoc analyses: Decrease in primary outcome in cohort with birth weight >1000 g; higher rate of mortality and severe IVH in cohort with birth wt <1000 g
Hascoet, 2005[18]	145	<32	—	6–48 h	aAO_2 ratio <0.22	5 ppm for first h of treatment and further dosage were adjusted based on response; total duration of treatment not clearly defined but varied from 4 h in nonresponders to few days in responders	Intact survival at 28 d	No difference in primary outcome; iNO was an independent risk factor for the combined risk of death or brain lesion
Field, 2005[19]	108	<34	—	<28 d; median 1 d	Severe respiratory failure requiring assisted ventilation	5–40 ppm depending on patient response; total duration of treatment not clearly defined	Death or severe disability at 1 y corrected age; death or CLD	No difference in primary outcome
Kinsella, 2006[20]	793	≤34	500–1250	<48 h	Need for mechanical ventilation	5 ppm for maximum of 21 d	Death or BPD at 36 wk postmenstrual age	No difference in primary outcome but had a decreased risk of brain injury; decreased incidence of BPD in cohort with birth weight ≤1000 g
Dani, 2006[21]	40	<30	—	≤7 d	aAO_2 ratio <0.15	10 ppm for 4 h then 6 ppm until extubation	Death and BPD	Primary outcome less with iNO treatment

TABLE 1 Continued

Author, Year	*n*	Gestational Age, wk	Birth Weight, g	Age at Enrollment	Entry Criteria	iNO Protocol	Primary Outcome	Study Results
Ballard, 2006[24]	582	≤32	500–1250	7–21 d	Need for mechanical ventilation for lung disease between 7 and 21 d; infants with birth weight 500–799 g were eligible if requiring nasal CPAP	20 ppm for 48–96 h followed by 10, 5, and 2 ppm at weekly intervals, with a minimum treatment duration of 24 d	Survival without BPD at 36 wk of postmenstrual age	Improved survival without BPD at 36 wk postmenstrual age; post hoc analysis showed most benefit when iNO treatment was started between 7–14 d of age
Van Meurs, 2007[23]	29	<34	>1500	4–120 h; mean 24–25 h	OI ≥15 on 2 consecutive blood gases between 30 min and 12 h apart	5–10 ppm for maximum of 14 d	Incidence of death or BPD	No difference in primary outcome
Su and Chen, 2008[22]	65	<32	≤1500	Mean 2.5 d	OI ≥25	5–20 ppm based on patient response; treatment duration at physician discretion (mean duration 4.9 ± 2.3 d)	OI at 24 h after randomization	Improved oxygenation with iNO treatment; no difference in survival, CLD, IVH, PDA, ROP, or duration of intubation
Mercier, 2010[25]	800	<29	>500	First day of life	Need for surfactant or CPAP within 24 h of birth	5 ppm for minimum of 7 d and maximum of 21 d	Survival without BPD at 36 wk postmenstrual age	No difference in primary outcome; no difference in survival alone; no difference in BPD; no difference in brain injury

Dash indicates not part of enrollment criteria.
aAO_2, arterial-alveolar oxygen ratio; CLD, chronic lung disease; CPAP, continuous positive airway pressure; IVH, intraventricular hemorrhage; OI, oxygenation index; PDA, patent ductus arteriosus; PVL, periventricular leukomalacia; ROP, retinopathy of prematurity.

of meta-analysis using aggregate data from different trials and to identify any patient or treatment characteristics that might predict benefit, Askie et al[9] conducted an individual-patient data meta-analysis. Data from 3298 infants in 11 trials that included 96% of published data showed no statistically significant effect of iNO on the rate of death or chronic lung disease (relative risk 0.96; 95% confidence interval 0.92–1.01) or severe brain lesions on cranial imaging (relative risk 1.12; 95% confidence interval 0.98–1.28). There were no statistically significant differences in iNO effect according to any of the patient-level characteristics tested; however, the authors cautioned that they could not exclude the possibility of a small reduction in the combined outcome of death or chronic lung disease if a higher dose of iNO (20 ppm) was used after >7 days of age, as observed in the NOCLD study.[9,24]

COST-BENEFIT ANALYSES OF ROUTINE USE OF INO IN PRETERM INFANTS

Treatment with iNO is expensive and can add significantly to health care costs.[8] A retrospective economic evaluation using patient-level data from the NOCLD trial (the only trial showing clinical benefit) reported that the overall mean cost per infant for the initial hospitalization was similar in the treated and placebo groups; however, when iNO therapy was initiated between 7 and 14 days of age, there was a 71% probability that the treatment decreased costs and improved outcomes.[45] Cost-benefit analysis from 2 other studies failed to show any cost-benefit.[37,39] Among preterm infants in the Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide trial, there was no difference in resource use and cost of care through the 4-year assessment.[37] Using more robust research methodology, including

data on postdischarge resource utilization and health-related quality of life evaluations, Watson et al[39] found that costs of care did not vary significantly by treatment arm through 1 year of age. Although quality-adjusted survival was slightly better with iNO therapy, the estimated incremental cost-effectiveness ratio was $2.25 million per quality-adjusted life year, with only a 12.9% probability that the incremental cost-effectiveness ratio would be less than $500 000 per quality-adjusted life year. Additionally, in subgroup analysis, total costs were significantly higher for the iNO-treated group in the smallest birth weight stratum (500–749 g).

SAFETY OF INO USE IN PRETERM INFANTS

The only information regarding the safety of iNO use in preterm infants is derived from the NOCLD trial.[46–49] The limited data suggest that iNO is safe and does not increase lung inflammation or oxidative stress.[46,48]

SUMMARY

1. The results of randomized controlled trials, traditional meta-analyses, and an individualized patient data meta-analysis study indicate that neither rescue nor routine use of iNO improves survival in preterm infants with respiratory failure (Evidence quality, A; Grade of recommendation, strong).[50]
2. The preponderance of evidence does not support treating preterm infants who have respiratory failure with iNO for the purpose of preventing/ameliorating BPD, severe intraventricular hemorrhage, or other neonatal morbidities (Evidence quality, A; Grade of recommendation, strong).
3. The incidence of cerebral palsy, neurodevelopmental impairment, or cognitive impairment in preterm infants treated with iNO is similar to that of control infants (Evidence quality, A).
4. The results of 1 multicenter, randomized controlled trial suggest that treatment with a high dose of iNO (20 ppm) beginning in the second postnatal week may provide a small reduction in the rate of BPD. However, these results need to be confirmed by other trials.
5. An individual-patient data meta-analysis that included 96% of preterm infants enrolled in all published iNO trials found no statistically significant differences in iNO effect according to any of the patient-level characteristics, including gestational age, race, oxygenation index, postnatal age at enrollment, evidence of pulmonary hypertension, and mode of ventilation.
6. There are limited data and inconsistent results regarding the effects of iNO treatment on pulmonary outcomes of preterm infants in early childhood.

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