CE 2.3 HOURS Continuing Education

Efficacy of Inhaled Nitric Oxide in Preterm Neonates

Lauren E. Love, MSN, RN, CNS, NNP-BC; Wanda T. Bradshaw, MSN, RN, NNP-BC

ABSTRACT

Over the past 20 years, the recognition of nitric oxide (NO) as an endothelial-derived vasodilator has led to remarkable advances in vascular biology awareness. The signaling molecule NO, produced by NO synthase, is a molecule that is widespread in the body and important in multiple organ systems. Soon after its discovery, investigators found NO to be a potent pulmonary vasodilator in term neonates. Nitric oxide has come to perform a key function in neonatal therapy and management since its identification, especially in those with respiratory failure. It is conventionally used in the neonatal population for the treatment of persistent pulmonary hypertension, resulting in hypoxic respiratory failure of the term or near-term newborn. Inhaled NO has been successful in acutely improving oxygenation and in reducing the need for extracorporeal membrane oxygenation treatment. In recent years, the efficacy of inhaled NO for the prevention of pulmonary disability as well as its neuroprotective capabilities in preterm infants has been explored.

KEY WORDS: brain injury, bronchopulmonary dysplasia, inhaled nitric oxide, intraventricular hemorrhage, neuroprotection, periventricular leukomalacia, preterm infants, respiratory distress syndrome

In preterm infants, neonates less than 37 weeks' gestation, with respiratory distress syndrome (RDS), poor ventilation-perfusion matching, and elevated pulmonary vascular resistance commonly present.[1] Both pulmonary artery pressure and oxygenation have been thought to improve with inhaled nitric oxide (iNO) therapy. Preterm infants are at risk for bronchopulmonary dysplasia (BPD), a long-term pulmonary disability in neonates characterized by inflammation and scarring in the lungs due to mechanical ventilation. If the hypothesis that the use of iNO therapy reduces required ventilator support, then consequential lung injury will decline and the frequency of BPD will follow.[2] Bronchopulmonary dysplasia is an extremely important chronic medical illness because it leads to arrested lung development in the neonate. It is a major cause of neonatal mortality and morbidity and is associated with neurodevelopmental impairment.[3] In addition to pulmonary effects, endogenously produced nitric oxide (NO) in the brain offers neuroprotection by regulating local blood flow.[4] The prospect of iNO therapy contributing to the secondary benefit of neuroprotection is also an exciting possibility. Increased permeability of the blood-brain barrier via the formation of free radicals such as peroxynitrites raised concern in previous studies.[5,6] Variation of circulating neutrophils, monocytes, and platelets as they enter the lung are a few ways iNO offers neuroprotection.[4] A strong relationship between brain injury and BPD or sepsis has been reported[7] most likely because of the systemic inflammatory response and the release of cytokines into the circulatory system that probably play a role in brain injury. Studies have demonstrated that iNO minimizes oxidant stress by the downregulation of lung-derived cytokines.[8,9] This breakthrough discovery may lead to a decline in brain injury.

Inhaled NO enhances pulmonary angiogenesis, lung alveolarization, distal lung development, and pulmonary performance in preterm infants as several studies indicate.[10] However, it still remains uncertain which subpopulations of infants might profit the most from iNO, given the inconclusive results of the clinical studies. There are also opposing data on whether exogenous NO is protective or destructive in the

Author Affiliation: *Duke University School of Nursing, Duke University Health System, Durham, North Carolina.*

Both authors have contributed equal substance to this work.

There are no conflicts of interest.

Correspondence: *Lauren E. Love, MSN, RN, CNS, NNP-BC, Duke University School of Nursing, Duke University Health Care System, Durham, NC 27710 (lauren.love@duke.edu).*

DOI: 10.1097/ANC.0b013e318242ddfc

presence of hyperoxia.[10] Inhaled NO minimizes oxidant stress by the downregulation of lung-derived cytokines, suggesting a possible decline in brain injury.[8,9] Hence, the purpose of this article is to determine the efficacy and safety of iNO therapy in preterm infants with severe RDS and respiratory failure along with its neuroprotectant factors. A literature review of all full-text, English language studies in PubMed, CINAHL, and the Cochrane Library between 2005 and 2010 was used.

Mechanism of Action

In its inhaled form, NO causes relaxation of smooth muscles and vasodilation.[11] This process is activated as iNO quickly diffuses from the alveolar space to the vascular smooth muscle cell, binding with and increasing cyclic guanosine monophosphate. This then triggers a surge of GMP-dependent protein kinases, resulting in an efflux of calcium from cells.[11] These pulmonary effects caused by iNO help uphold normal vascular permeability and maintain low pulmonary arterial pressures. Inhaled NO helps decrease ventilation-perfusion mismatch and improve oxygenation because it restructures pulmonary blood flow as it is preferentially carried to ventilated areas of the lung.[12] In a dose-dependent manner, NO systemically disrupts platelet and leukocyte functions, increasing and decreasing the inflammatory processes, and also increases urine output. But, these systemic vascular effects have demonstrated to be insignificant and iNO adverse effects are uncommon.[12] Miller and Rhine[12] describe iNO toxicity as the formation of methemoglobin, hemoglobin whose iron component is altered so that it does not carry oxygen well, nitric dioxide, a potent oxidant, and peroxynitrite, a powerful oxidant and proinflammatory mediator. Life-threatening adverse effects of acute withdrawal from iNO include rebound pulmonary hypertension and hypoxemia. Inhaled NO must be weaned slowly.

Background

In the term and late preterm infants, iNO has been used for the treatment of persistent pulmonary hypertension with hypoxic respiratory failure.[11] In preterm infants with respiratory failure secondary to RDS and other pulmonary diseases, it was considered for use soon thereafter. According to Miller and Rhine,[12] RDS seen in prematurity is linked with postponed postnatal circulatory adaptation characterized by pulmonary hypertension, systemic hypotension, and prolonged ductus arteriosus patency. Martin and Walsh[13] proposed that iNO may have several effects on the developing lung parenchyma, bronchi, and vasculature between 25 and 28 weeks' gestation. Proposed effects include increased growth and surfactant function with decreased elastin production and inflammation, increased bronchodilation, and decreased airway smooth muscle proliferation.[13] Ballard and colleagues[14] discovered that iNO may, in fact, improve surfactant function briefly in infants weighing less than 1250 g receiving a lengthy course of iNO. No evidence of adverse effects is detected in iNO therapy outcomes on surfactant protein composition and recovery. The concern for possible development or progression of intraventricular hemorrhage (IVH) in the delicate premature brain must also be considered, given the consequences of iNO therapy on platelet function.[15]

Animal Studies

To better understand the various roles that iNO may have in the developing lung, animal studies were preformed. A study performed in a premature rat model with BPD demonstrated that iNO therapy prolonged survival, decreased fibrin deposition, enhanced alveolar growth by lessening septal thickness, and reduced the influx of leukocytes and capillary-alveolar leakage.[16] Inhaled NO–induced downregulation of genes affecting inflammation, coagulation, fibrinolysis, and cell cycle regulation has been confirmed in mRNA testing as well as fibroblast growth factor receptor-4 upregulation. This type of fibroblast growth factor membrane receptor is involved in secondary septation and alveolar enlargement.[16]

Continuous, low-dose iNO therapy administered immediately after birth to a BPD lamb model for an extended 3-week course of mechanical ventilation showed significantly decreased airway resistance, less airway smooth muscle growth, and greater alveolarization but detected no variance in pulmonary vascular resistance.[17] This study revealed iNO augments alveolar development, while preserving composition and function of airway smooth muscle. Premature infants with BPD can be greatly influenced by both of these actions.

McCurnin and colleagues[18] performed a study in a baboon model of BPD. At the end of the study, these researchers observed that beginning iNO in premature baboons within 1 hour of life and sustaining it for 14 days resulted in decreased pulmonary artery pressure, larger incidence of spontaneous closure of the ductus arteriosus, better lung compliance and expiratory resistance, and increased lung DNA content and cell proliferation, and maintained lung growth. Possible modification of alveolarization by iNO was suggested in the study as the excessive elastin was normalized and secondary neural crest cell development was present.[18]

Human Studies

A Cochrane meta-analysis of all randomized and quasi-randomized studies in preterm babies with

respiratory disease has been published comparing the administration effects of iNO on a control group, with and without placebo gas.[2] Although the preferred approach to evaluate the value of a given treatment is a meta-analysis, the differing characteristics of all the trials are a limiting factor to its usefulness.[19] There is a wide spectrum of studies regarding iNO use in the preterm neonate ranging from rescue therapy of hypoxic respiratory failure because of persistent pulmonary hypertension of the newborn or severe BPD to a prophylactic use in order to prevent BPD.[2] The trials to date can be grouped into 3 different categories, depending on the entry criteria for iNO use: initiation within the first 3 days of life based on oxygen criteria, also termed as rescue therapy, routine use in preterm intubated patients, or later enrollment based on an increased risk for BPD (see Table 1).

The multicenter study headed by Van Meurs et al[15] randomly assigned neonates less than 34 weeks' gestation, with a birth weight of 401 to 1500 g, and with respiratory failure more than 4 hours after treatment with surfactant to iNO at 5 to 10 parts per million (ppm) or placebo gas. The incidence of death or BPD was 80% in the iNO-treated group compared with 82% in the placebo group, and the rate of BPD alone was 60% in the iNO-treated group versus 68% in the placebo group. Death and BPD rates were reduced for infants with birth weights greater than 1000 g without an increase in the rate of IVH as suggested in the post hoc analyses, whereas infants who were treated with iNO and weighed 1000 g or less had a higher mortality and increased rate of severe intracranial hemorrhage.[15] At the recommendation of the data safety and monitoring committee, the study was terminated early as the frequency of severe IVH or periventricular leukomalacia (PVL) appeared to be significantly greater in the treatment group with no benefit on the primary outcome of reducing rates of BPD or death.[12] This difference was not statistically significant at the end of the trial.

TABLE 1. Comparison Inhaled NO Compared to Control, Outcome Death, or Bronchopulmonary Dysplasia at 36 Wk[a]

Study or Subgroup	Treatment (n/N)	Control (n/N)	*P* Relative Risk [95% CI]
Studies with entry before 3 d based on oxygenation[b]			
Franco-Belgium Collaborative NO Trial Group 1999[25]	18/40	24/45	0.84 [0.54-1.31]
Hascoet et al 2005[26]	33/57	41/74	1.04 [0.77-1.41]
Van Meurs et al[15]	167/210	168/210	0.99 [0.90-1.09]
Dani et al 2006[27]	10/20	18/20	0.56 [0.35-0.88]
Field et al 2005[28]	49/55	48/53	0.98 [0.87-1.12]
Kinsella et al 1999[29]	37/48	29/32	0.85 [0.70-1.03]
Su and Chen 2007[30]	16/32	21/33	0.79 [0.51-1.21]
Van Meurs et al 2007[31]	7/14	9/15	0.83 [0.43-1.62]
Subtotal (95% CI)	476	482	0.94 [0.87-1.01]
Studies with entry after 3 d based on BPD risk[c]			
Ballard et al[14]	165/294	182/288	0.89 [0.78-1.02]
Subhedar and Shaw 1997[32]	20/20	21/22	1.04 [0.92-1.19]
Subtotal (95% CI)	314	310	0.90 [0.80-1.02]
Studies of routine use in intubated preterm infants[d]			
Kinsella et al[20]	282/398	295/395	0.95 [0.87-1.03]
Schreiber et al 2003[33]	51/105	65/102	0.76 [0.60-0.97]
Mercier et al 2009[34]	139/401	141/399	0.98 [0.81-1.18]
Subtotal (95% CI)	904	896	0.93 [0.86-1.01]

Abbreviation: CI, confidence interval; NO, nitric oxide.

[a]Review: Inhaled nitric oxide for respiratory failure in preterm infants. Comparison: Inhaled nitric oxide compared to control. Outcome: Death or bronchopulmonary dysplasia at 36 wk.

[b]Total events: 337 (treatment), 358 (control). Heterogeneity: $\chi^2 = 9.43$, $df = 7$ ($P = .22$); $I_2 = 26\%$. Test for overall effect: $Z = 1.73$ ($P = .084$).

[c]Total events: 185 (treatment), 203 (control). Heterogeneity: $\chi^2 = 5.04$, $df = 1$ ($P = .02$); $I_2 = 80\%$. Test for overall effect: $Z = 1.65$ ($P = .099$).

[d]Total events: 472 (treatment), 501 (control). Heterogeneity: $\chi^2 = 3.03$, $df = 2$ ($P = .22$); $I_2 = 34\%$. Test for overall effect: $Z = 1.70$ ($P = .090$).

Eleven rescue treatment trials were compared in the Cochrane meta-analysis.[2] The results of the meta-analysis of this subgroup showed identical findings to the study by Van Meurs et al.[15] The analysis showed no significant effect on survival to discharge, death prior to 36 weeks' postmenstrual age, incidence of BPD, combined outcome of death or BPD, or overall IVH frequency. Although the effect was not significant upon conclusion, the studies showed a movement toward increased incidence of severe IVH, defined as grades 3 and 4, and in PVL as well. Moreover, improvement in oxygenation was noted within 2 hours of the iNO therapy initiation by multiple studies.[2]

Within the past 5 years, only 1 study has been done regarding the routine use of iNO in preterm infants. The study by Kinsella and colleagues[20] enrolled newborns who were 34 weeks' gestational age or less and had respiratory failure requiring mechanical ventilation. Newborns were randomly assigned to receive either iNO (5 ppm) or placebo gas for 21 days or until extubation, with stratification according to birth weight (500 to 749 g, 750 to 999 g, or 1000 to 1250 g). A composite of death or BPD at 36 weeks' postmenstrual age was the primary efficacy outcome. Intracranial hemorrhage, PVL, and ventriculomegaly were secondary safety outcomes of the study. The incidence of death or BPD between patients receiving iNO and those receiving placebo showed no significant difference (71.6% vs 75.3%, $p = .24$). However, when comparing treatment and placebo in infants weighing between 1000 and 1250 g at birth, iNO therapy showed a reduction in the incidence of BPD (29.8% vs 59.6%, $p = .001$). Inhaled NO treatment did reduce the combined end point of intracranial hemorrhage, PVL, or ventriculomegaly (17.5% vs 23.9%, $p = .03$) and of PVL alone (5.2% vs 9.0%, $p = .048$). Overall, low-dose iNO did not reduce the incidence of BPD among premature infants with respiratory failure, except among infants with a birth weight of at least 1000 g, but it did reduce the overall chance of brain injury[20] (see Table 2).

The final category of the later enrollment based on BPD-risk subgroup defines Ballard and colleagues'[14] study. The trial was a multicenter, randomized, stratified, double-blind, placebo-controlled trial of iNO involving infants with a birth weight of 1250 g or less requiring ventilator support between 7 and 21 days of age. For a minimum of 24 days, treated infants received decreasing concentrations of NO. Survival without BPD at 36 weeks' postmenstrual age was the primary outcome of the study. The rate of survival without BPD at 36 weeks' postmenstrual age was 43.9% in the group receiving NO and 36.8% in the placebo group ($p = .042$). The infants who were treated with iNO received supplemental oxygen therapy for a shorter time ($p = .006$) and were

TABLE 2. Incidence of Death or Bronchopulmonary Dysplasia at 36 wk of Postmenstrual Age

Variable Risk	Inhaled Nitric Oxide (N = 398), n/N (%)	Placebo (N = 395), n/N (%)	*P* Relative	(95% CI)
All patients				
Death	78/394 (19.8)	98/392 (25.0)	0.08	0.79 (0.61–1.03)
Bronchopulmonary dysplasia	212/326 (65.0)	210/309 (68.0)	0.43	0.96 (0.86–1.09)
Death or bronchopulmonary dysplasia	282/394 (71.6)	295/392 (75.3)	0.24	0.95 (0.87–1.03)
Birth weight of 500–749 g				
Death	55/191 (28.8)	66/189 (34.9)	0.20	0.82 (0.61–1.11)
Bronchopulmonary dysplasia	113/144 (78.5)	100/132 (75.8)	0.59	1.04 (0.91–1.18)
Death or bronchopulmonary dysplasia	162/191 (84.8)	159/189 (84.1)	0.85	1.01 (0.92–1.10)
Birth weight of 750–999 g				
Death	15/138 (10.9)	24/139 (17.3)	0.13	0.63 (0.35–1.15)
Bronchopulmonary dysplasia	82/125 (65.6)	76/120 (63.3)	0.71	1.04 (0.86–1.25)
Death or bronchopulmonary dysplasia	95/138 (68.8)	95/139 (68.3)	0.93	1.01 (0.86–1.18)
Birth weight of 1000–1250 g				
Death	8/65 (12.3)	8/64 (12.5)	0.97	0.98 (0.39–2.46)
Bronchopulmonary dysplasia	17/57 (29.8)	34/57 (59.6)	0.001	0.50 (0.32–0.79)
Death or bronchopulmonary dysplasia	25/65 (38.5)	41/64 (64.1)	0.004	0.60 (0.42–0.86)

Abbreviation: CI, confidence interval.

discharged sooner ($p = .04$). The study confirmed that iNO therapy in premature infants improves the pulmonary outcome for those who are at risk for BPD when it is initiated between 7 and 21 days of age and has no evident short-term adverse effects.[14]

Neurodevelopmental Outcomes

Preterm infants are at a high risk for neurodevelopmental impairment, including blindness, deafness, cerebral palsy, and global cognitive delay,[21] as well as more subtle cognitive deficits, such as language delay, learning disabilities, and attention and executive function abnormalities.[4] Little progress has been made in developing treatments or creating preventative measures, despite an increasing awareness of the risk factors leading to abnormal neurodevelopmental outcomes. The impact of iNO remains controversial in regard to the development of the central nervous system. In past studies, an increase was noted in the incidence of intracranial hemorrhage in critically ill preterm neonates receiving iNO therapy.[15] Nitric oxide was demonstrated to increase bleeding time and inhibit platelet aggregation in many initial iNO trials.[19] Although a trend for an increased incidence of severe IVH or PVL was noted in early rescue studies, there was no significant difference between control and iNO groups.[4] The varied entry criteria, lack of cranial ultrasound scans before study entry, short duration of iNO treatment, and more critically ill babies being enrolled in these trials are examples of the limitations to analyses of the results. In comparison with the early rescue trials, the early prophylactic trials showed a reduction of neurological injury while the late therapy trials showed no progression of this outcome.

The study by Mestan and colleagues[22] noted a momentous decrease in the composite outcome of neurodevelopmental disability, defined as cerebral palsy, bilateral blindness, bilateral hearing loss, and greater than 2 SD lower than the mean of Bayley scores of infant development. There were more mature and fewer critically ill neonates in this single-center study who were not at high risk for this outcome. Nevertheless, this is the first trial to date to report 2-year follow-up of iNO therapy outcomes on neurodevelopmental status giving reassurance of no potential harm with iNO in this patient population.

The results of the Neonatal Ventilation With Inhaled Nitric Oxide Versus Ventilatory Support Without Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure study, also known as the INNOVO trial for short, by Huddy et al[23] were still pending when the results of the Mestan et al[22] study were released. When the INNOVO study was published, its investigators reported the rates of major disability from iNO therapy given to ventilated premature infants at 1 year of age weighing less than 1250 g, which showed no difference between the groups. *Severe disability* was defined as no/minimal head control or inability to sit unsupported or no/minimal responses to visual stimuli. There was no difference between the groups (7 of the 55 patients who received iNO therapy vs 2 of the 53 patients who did not receive iNO therapy could not sit unsupported at 1 year).

The most recent study to date by Walsh and colleagues[24] reported follow-up neurodevelopmental outcomes at 2 years of age in ventilated preterm infants treated with iNO. The study concluded that exposure to 24 days of iNO treatment initiated at 20 ppm between 7 and 21 days in ventilated preterm infants is both safe and effective, with improved survival free of BPD and no adverse effects on growth or neurodevelopmental status at 2 years of age.[24]

Conclusion

Despite the thousands of babies being enrolled in iNO trials, there are still questions to be answered about clinical management of iNO in preterm newborns. The available data for the use of iNO in the management of preterm neonates suggest that a beneficial effect depends on the patient population, duration of therapy, and underlying pathological condition.[4] The early and late uses of iNO in the management of preterm neonates cannot be recommended until BPD results and long-term neurodevelopmental follow-up data show consistent, beneficial findings. The use of iNO as rescue therapy for infants weighing less than 1 kg is confounded by a patient population at high risk for an adverse neurological outcome. Although endogenous NO is important for lung growth, there is little evidence that an exogenous supply of NO achieves that goal. Only in a small population of infants weighing between 1000 and 1250 g at birth did iNO therapy in one study show a reduction in the incidence of BPD.[20] The potential role of iNO needs to be further defined and the abundant laboratory evidence needs to be translated to beneficial clinical outcomes before it can be used by health care providers as a standard of care.

References

1. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. *J Perinatol.* 2008;28(2):112-116. doi:10.1038/sj.jp.7211881
2. Barrington KJ, Finer NN. Inhaled nitric oxide for respiratory failure in preterm infants. *Cochrane Database Syst Rev.* 2007;(3):CD000509. doi:10.1002/14651858.CD000509.pub3.
3. Vohr BR, Wright LL, Poole WK, et al. Neurodevelopmental outcomes of extremely low birth weight infants <32 weeks gestation between 1993 and 1998. *Pediatrics.* 2005;116(3):635-643. doi:10.1542/peds.2004-2247
4. Arul N, Konduri GG. Inhaled nitric oxide for preterm neonates. *Clin Perinatol.* 2009;36(1):43-61. doi:10.1016/j.clp.2008.09.002
5. Martin RJ. Nitric oxide for preemies—not so fast. *N Engl J Med.* 2003;349(22):2157-2159.
6. Mayhan WG. Nitric oxide donor–induced increase in permeability of the blood-brain barrier. *Brain Res.* 2000;866(1/2):101-108. doi:10.1016/S0006-8993(00)02254-X
7. Viscardi RM, Muhumuza CK, Rodriguez A, et al. Inflammatory markers in intrauterine and fetal blood and cerebrospinal fluid compartments are associated with adverse pulmonary and neurologic outcomes in preterm infants. *Pediatr Res* 2004;55:1009-1017. doi:00313998/04/5506-1009
8. Haynes RL, Baud O, Li J, et al. Oxidative and nitrative injury in periventricular leukomalacia: a review. *Brain Pathol.* 2005;15:225–233. doi:10.1111/j.1750-3639.2005.tb00525.x

9. Aaltonen M, Soukka H, Halkola L, et al. Inhaled nitric oxide treatment inhibits neuronal injury after meconium aspiration in piglets. *Early Hum Dev.* 2007;83:77–85. doi:10.1016/j.earlhumdev.2006.05.003
10. Rieger-Fackeldey E, Hentschel R. Bronchopulmonary dysplasia and early prophylactic inhaled nitric oxide in preterm infants: current concepts and future research strategies in animal models. *J Perinat Med.* 2008;36(5):442-447. doi:10.1515/JPM.2008.065
11. Soll RF. Inhaled nitric oxide in the neonate. *J Perinatol.* 2009;29(suppl 2):S63-S67. doi:10.1038/jp.2009.40
12. Miller SS, Rhine DW. Inhaled nitric oxide in the treatment of preterm infants. *Early Hum Dev.* 2008;84(11):703-707. doi:10.1016/j.earlhumdev.2008.08.005
13. Martin RJ, Walsh MC. Inhaled nitric oxide for preterm infants—who benefits? *N Engl J Med.* 2005;353(1):82-84.
14. Ballard RA, Truog WE, Cnaan A, et al. Inhaled nitric oxide in preterm infants undergoing mechanical ventilation. *N Engl J Med.* 2006;355(4):343-353.
15. Van Meurs KP, Wright LL, Ekrenkranz RA, et al. Inhaled nitric oxide for premature infants with severe respiratory failure. *N Engl J Med.* 2005;353(1):13-22.
16. ter Horst SAJ, Walther FJ, Poorthuis BJHM, et al. Inhaled nitric oxide attenuates pulmonary inflammation and fibrin deposition and prolongs survival in neonatal hyperoxic lung injury. *Am J Physiol Lung Cell Mol Physiol.* 2007;293(1):L35-L44. doi:10.1152/ajplung.00381.2006
17. Bland RD, Albertine KH, Carlton DP, et al. Inhaled nitric oxide effects on lung structure and function in chronically ventilated preterm lambs. *Am J Respir Crit Care Med.* 2005;172(7):899-906. doi:10.1164/rccm.200503-384OC
18. McCurnin DC, Pierce RA, Chang LY, et al. Inhaled NO improves early pulmonary function and modifies lung growth and elastin deposition in a baboon model of neonatal chronic lung disease. *Am J Physiol Lung Cell Mol Physiol.* 2005;288(3):L450-L459. doi:10.1152/ajplung.00347.2004
19. Mercier JC, Olivier P, Loron G, et al. Inhaled nitric oxide to prevent bronchopulmonary dysplasia in preterm neonates. *Semin Fetal Neonatal Med.* 2009;14(1):28-34. doi:10.1016/j.siny.2008.08.009
20. Kinsella JP, Cutter GR, Walsh WF, et al. Early inhaled nitric oxide therapy in premature newborns with respiratory failure. *N Engl J Med.* 2006;355(4):354-364. doi:10.1056/NEJMoa060442
21. Marks JD, Schreiber MD. Inhaled nitric oxide and neuroprotection in preterm infants. *Clin Perinatol.* 2008;35(4):793-807, viii. doi:10.1016/j.clp.2008.07.015
22. Mestan KK, Marks JD, Hecox K, Huo D, Schreiber MD. Neurodevelopmental outcomes of premature infants treated with inhaled nitric oxide. *N Engl J Med.* 2005;353(1):23-32.
23. Huddy CL, Bennett CC, Hardy P, et al. The INNOVO multicentre randomized controlled trial: Neonatal ventilation with inhaled nitric oxide versus ventilator support without nitric oxide for severe respiratory failure in preterm infants: Follow up at 4–5 years. *Arch Dis Child Fetal Neonatal Ed.* 2008;93(6):F430-F435. doi:10.1136/adc.2007.129353
24. Walsh MC, Hibbs AM, Martin CR, et al. Two-year neurodevelopmental outcomes of ventilated preterm infants treated with inhaled nitric oxide. *J Pediatr.* 2010;156(4):556.e1-561.e1. doi:10.1016/j.jpeds.2009.10.011
25. Franco-Belgium Collaborative NO Trial Group. Early compared with delayed inhaled nitric oxide in moderately hypoxaemic neonates with respiratory failure: a randomized controlled trial. *Lancet.* 1999;354:1066–1071. doi:10.1016/S01406736(99)03309-7
26. Hascoet JM, Fresson J, Claris O, Hamon I, Lombet J, Liska A, et al. The safety and efficacy of nitric oxide therapy in premature infants. *J Pediatr.* 2005;146:318–323. doi:10.1016/j.jpeds.2004.10.019
27. Dani C, Bertini G, Pezzati M, Filippi L, Cecchi A, Rubaltelli FF. Inhaled nitric oxide in very preterm infants with severe respiratory distress syndrome. *Acta Paediatr.* 2006;95:1116–1123. doi: 10.1080/08035250600702594
28. Field D, Elbourne D, Truesdale A, Grieve R, Hardy P, Fenton AC, et al. Neonatal ventilation with inhaled nitric oxide versus ventilatory support without inhaled nitric oxide for preterm infants with severe respiratory failure: the INNOVO multicentre randomized controlled trial (ISRCTN 17821339). *Pediatr.* 2005;115:926–936. doi: 10.1542/peds.2004-1209
29. Kinsella JP, Walsh WF, Bose CL, Gerstmann DR, Labella JJ, Sardesai S. Inhaled nitric oxide in premature neonates with severe hypoxaemic respiratory failure: a randomized controlled trial. *Lancet.* 1999;354:1061–1065. doi:10.1016/S0140-6736(99)03558-8
30. Su PH, Chen JY. Inhaled nitric oxide in the management of preterm infants with severe respiratory failure. *J Perinatol.* 2008;28:112–116. doi:10.1038/sj.jp.7211881
31. Van Meurs KP, Hintz SR, Ehrenkranz RA, Lemons JA, Ball MB, Poole WK, et al. Inhaled nitric oxide in infants >1500 g and <34 weeks gestation with severe respiratory failure. *J Perinatol.* 2007;27:347–352. doi:10.1038/sj.jp.7211690
32. Subhedar NV, Shaw NJ. Changes in oxygenation and pulmonary haemodynamics in preterm infants treated with inhaled nitric oxide. *Arch Dis Child Fetal Neonatal Ed.* 1997;77:F191–F197. doi:10.1136/fn.77.3.F191
33. Schreiber MD, Gin-Mestan K, Marks JD, Huo D, Lee G, Srisuparp P. Inhaled nitric oxide in premature infants with the respiratory distress syndrome. *N Engl J Med.* 2003;349:2099–2107.
34. Mercier JC, Hummler H, Durrmeyer X, Sanchez-Luna M, Carnielli V, Field D, et al. Inhaled nitric oxide for the prevention of bronchopulmonary dysplasia in premature babies (EUNO): a randomized controlled trial. *Lancet.* 2010;376:346–354. doi:10.1016/S0140-6736(10)60664-2