Inhaled Nitric Oxide Therapy in Neonatal Hypoxic Respiratory Failure: Insights Beyond Primary Outcomes

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The Neonatal Research Network developed and initiated 3 multicenter randomized controlled clinical trials evaluating inhaled nitric oxide therapy. Additional projects evolved from these efforts including basic science research and observational investigations. This article provides a historical perspective of the Network’s investigations related to the diagnosis and management of neonatal hypoxic respiratory failure, especially those related to inhaled nitric oxide therapy. It will review the Network’s contributions toward advancing the clinical care of the newborn with severe hypoxic respiratory failure.

Persistent pulmonary hypertension of the newborn (PPHN) is a rare and potentially life-threatening condition first described in 1969.1 It exists as a distinct disorder or as a complication of other respiratory disorders, such as meconium aspiration syndrome, bacterial pneumonia, respiratory distress syndrome (RDS), or congenital diaphragmatic hernia (CDH).2,3 Since elevated pulmonary pressures contribute to right-to-left shunt resulting in profound hypoxemia, clinicians have sought a pulmonary vasodilator without systemic effects. The identification of endothelial derived relaxing factor as the gas, nitric oxide, raised hopes that such a specific pulmonary vasodilator had been identified.4-6 The first clinical reports of inhaled nitric oxide (iNO) therapy in neonates appeared in 1992; the rapid improvements in oxygenation led to hopes that this noninvasive therapy could reduce the need for extracorporeal membrane oxygenation (ECMO) in infants with hypoxic respiratory failure who were failing conventional therapy.7,8

In the early 1990s, there were several major obstacles impeding clinical investigation of iNO therapy. First, the lack of a tested, approved iNO delivery and monitoring system forced investigators to devise and assemble a safe iNO delivery and monitoring system. Second, there was no consensus of the optimal medical management of PPHN and limited objective knowledge of patient outcomes. Finally, the pervasive clinical use of unproven therapies in this patient population was perhaps the greatest obstacle.

Prior to the clinical investigation of iNO therapy, the majority of treatments for PPHN were rapidly introduced into clinical practice with limited evaluation. The clinical use of unproven therapies is a frequent and often unavoidable dilemma in medical practice, especially in critical care.9 Promising, yet unsubstantiated, high-technology therapies such as high frequency ventilation and ECMO rapidly diffused into practice, while low-tech approaches with potential (gentle ventilation) were overlooked.10 As the National Institute of Child Health and Human Development’s (NICHD) Neonatal Research Network contemplated a multi-center clinical trial evaluating iNO therapy, an understanding of the current management practices for this disease process was essential.

Persistent Pulmonary Hypertension of the Newborn in the Era Before Nitric Oxide: Practice Variation and Outcomes

Concurrent with the development of a large, multi-center, randomized controlled-clinical trial investigating the clinical use of iNO therapy in
the term and near-term neonate, the Network pursued a prospective investigation to describe the then current understanding of the disease, including its demographics, treatments, and outcomes. This prospective descriptive study was conducted between October 1993 and December 1994 at the 12 Network Centers prior to the widespread use of iNO therapy. Neonates who were ≥34 weeks’ gestation and <7 days of age were included if they were on mechanical ventilation with a FiO2 > 0.50 and demonstrated pulmonary artery hypertension via echocardiography or a preductal to postductal oxygen gradient >20 torr.

The observational study revealed that the prevalence of PPHN was 1.9 per 1,000 live births. Infants with the diagnosis of PPHN had a mean birth weight of 3.3 ± 0.6 kg with a mean gestational age 39 ± 2 weeks. Fifty-eight percent were male, 49% white, 33% black, and 19% other. Fetal heart rate abnormalities, meconium-stained amniotic fluid, cesarean section, and low Apgar scores were common. Seventy-seven percent of the patients with PPHN were identified within the first 24 hours of life, with 93% and 97% being diagnosed within 48 and 72 hours respectively. The respiratory diagnoses associated with PPHN were meconium aspiration syndrome (41%), idiopathic pulmonary hypertension (17%), pneumonia (14%), pneumonia/RDS (when the 2 could not be distinguished) (14%), RDS (13%), CDH (10%) and pulmonary hypoplasia (4%). Overall, survival was 88%, however survival in patients with CDH was only 61%.

Numerous therapies were employed to treat PPHN at the different centers including hyperventilation, alkali infusion, inotrope administration, paralysis, sedation, intravenous vasodilators, surfactant, high frequency ventilation, iNO and ECMO. Despite appreciable variability in the utilization of treatments between centers, there was no significant difference in survival between centers and no individual therapy was associated with a reduced risk of death. The investigators speculated that because ECMO was available to any patient failing a therapy or therapies, mortality was minimized. Therefore studies that evaluate therapies for PPHN, when ECMO is available as a rescue therapy, must use outcome measures other than mortality to assess the efficacy of the treatment. These observations helped to legitimize the “use of ECMO” as a valid outcome measure in future clinical trials investigating iNO therapy.

Two of the evaluated therapies, paralysis and ECMO were associated with an increased risk of death, while high frequency ventilation demonstrated a trend toward increased mortality. Subgroup analyses that excluded patients with CDH substantially reduced this mortality risk, suggesting that the increased mortality was largely explained by the severity of illness in the patients with CDH. The study also noted that alkali infusion was associated with increased use of ECMO and oxygen supplementation at 28 days of age and therefore not equivalent to hyperventilation.

### Nitrogen Dioxide Formation During Inhaled Nitric Oxide Therapy

Prior to the identification of an industry sponsor or a Federal Drug Administration (FDA) approved delivery system, clinical investigators faced the dilemma of developing a safe, accurate iNO delivery and monitoring system. Whenever NO and oxygen meet, a more toxic compound NO2 will be formed (see Equation 2: rate expression for NO2 formation). NO2 is a toxic gas and the Occupational Safety and Health Administration limits human peak exposure to 5 ppm.12 However, alterations in airway reactivity in humans have been reported at exposures as low as 1.5 ppm.13 To avoid toxicity, continuous monitoring of NO/NO2 concentrations remains essential. Introducing NO into the humid, high oxygen environment of a neonatal ventilator circuit revealed the limitations of the environmental NO/NO2 monitoring equipment. Reports of negative NO2 readings were common and the adequacy of the current technology was questioned.14,15 Several investigators reported or calculated NO2 formation during iNO therapy and estimates varied considerably.15-20 Before introducing iNO therapy into large multi-center clinical trials, the potential for NO2 toxicity needed to be precisely investigated.

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d\left[NO_2\right]/dt = 2k\left[NO\right]^{2}\left[O_2\right]
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(1)

To accurately measure NO2 formation under clinical conditions, the NICHD recruited the collaboration of the Analytical Chemistry Division of the National Institute of Standards and
Technology (NIST). Tunable diode laser absorption spectroscopy allowed the accurate measurement of NO2 in a NO and oxygen enriched matrix. Using a continuous flow, humidified conventional mechanical ventilator circuit at the clinically relevant conditions of 80 ppm NO with an FiO2 of 0.9, the rate of NO2 formation was determined to be \( \sim 0.14 \) ppm/s of dwell time.21 This rate of formation of NO2 was similar to that described in the atmospheric chemistry literature and provided reassurance that NO2 formation during iNO therapy could be accurately described and calculated using existing chemical kinetics and rate constants. At the lower NO concentrations currently used in clinical iNO therapy, the rate of NO2 formation is exponentially reduced secondary to the second-order dependence on NO concentration.

This investigation resulted in the development of important safety recommendations for the upcoming masked, randomized Network trials.22 To minimize NO2 exposure, continuous flow ventilator systems using flow rates of at least 10 lpm and injection of NO approximately 20 cm proximal to the patient connect were utilized to allow for adequate gas mixing while minimizing circuit dwell time and NO2 production. Additional safety precautions included using NIST certified calibration gases, vacuum purging of regulators (to minimize any potential for accidental NO source cylinder contamination) and flushing the NO delivery circuit through the ventilator exhaust circuit prior to connecting the NO delivery circuit to the patient inspiratory circuit (to rid NO2 buildup from within the delivery system).

Inhaled Nitric Oxide in Full-term and Nearly Full-term Infants With Hypoxic Respiratory Failure

In April of 1993, the National Heart, Lung, and Blood Institute (NHLBI) organized a workshop on NO.25 At this conference, basic science researchers met with clinicians and shared data about NO. The groundwork was laid for large randomized clinical trials investigating iNO therapy. Then in December 1993, the NICHD in conjunction with the NHLBI and FDA organized a second conference discussing the NO clinical trials in progress and under development. The designs of two of the investigations, the Canadian Inhaled Nitric Oxide Study and the proposed NICHD Neonatal Network study were similar, and following the meeting, those investigators combined their efforts to perform the Neonatal Inhaled Nitric Oxide Study.

The Neonatal Inhaled Nitric Oxide Study (NINOS) group was a collaboration effort between investigators of the NICHD Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group. Their main objective was to expeditiously establish the safety and efficacy of iNO therapy before that therapy diffused into standard clinical practice. The release of numerous individual Investigational New Drug (IND) numbers was allowing iNO therapy to rapidly diffuse into neonatal clinical practice. The data would also need to be of sufficient quality to be used for regulatory approval of the therapy. It was clear from discussions with the FDA that physiologic endpoints such as improvement in oxygenation would not be sufficient for regulatory approval. Although favored by the FDA, mortality was considered an unacceptable outcome for iNO trials given the availability of ECMO. Subsequently, the surrogate outcome of “the need for ECMO” was accepted as the most appropriate outcome to demonstrate efficacy of iNO therapy. The importance of monitoring neurodevelopmental follow-up with the introduction of a new therapy into the neonatal period and the need to identify toxicity precluded the use of a crossover design in this clinical investigation.

The primary hypothesis of the NINOS trial was that administration of iNO to infants \( \geq 34 \) weeks of gestation who had hypoxic respiratory failure would reduce the risk of death (by day 120) or the initiation of ECMO from 50% in control infants to 30% in infants treated with iNO (a relative reduction of 40%).24 A sample size of 250 infants, 125 in each group, was required to test this hypothesis. With “need for ECMO” an outcome measure, all prospective candidates for the investigation had to be eligible to receive ECMO therapy if needed. Therefore the 34-week or greater gestational age limitation was instituted. With limited human safety data, the trial focused on a population with significant morbidity, targeting patients with a 50% chance or greater of needing ECMO or dying. An oxygenation index \( (OI) = (\text{mean airway pressure x } \text{(mean airway pressure } x \text{FiO2)} \times 100) \) was used as a measure of oxygenation. The primary endpoint of the trial was the need for ECMO by day 120. The treatment was administered via a catheter placed into the trachea or endotracheal tube. The iNO dose was based on the patient’s weight and FiO2, with a dose of 150-200 ppm of NO being administered. The study was terminated early due to the observed reduction in the need for ECMO and mortality in the iNO group. The results of the NINOS trial provided important safety data and established the efficacy of iNO therapy for infants with hypoxic respiratory failure.
FiO$_2 \times 100)/P_{aO_2} \geq 25$ was believed to suggest that level of risk.

Patients were included if they suffered from hypoxic respiratory failure caused by meconium aspiration, PPHN, pneumonia or sepsis, RDS, or suspected pulmonary hypoplasia associated with oligohydramnios and premature rupture of membranes. Patients with CDH were enrolled in a concurrent parallel trial. Echocardiographic evidence of pulmonary hypertension was not required as entry criteria as iNO improves oxygenation by enhancing ventilation-perfusion matching. This approach was consistent with the fact that ECMO support is provided to neonates with or without evidence of pulmonary hypertension who are failing conventional management for hypoxic respiratory failure.

Given the known practice variations in the management of PPHN, it was deemed impossible to devise a regimented pre-randomization treatment strategy to which the 19 participating centers could agree. Nonetheless, each center established specific patient management guidelines to optimize conventional therapy prior to randomization. Administration of surfactant prior to randomization was encouraged. High frequency ventilation was allowed if initiated prior to randomization. This approach adhered to the philosophy that if iNO therapy benefited patients, it should do so under the diverse conditions under which it would be implemented in the real world (a pragmatic explanatory trial).

After about 2 years and randomization of 235 of the target study population of 250 patients, the second planned Data Safety and Monitoring Committee review recommended terminating the trial because of efficacy. The principal investigators agreed that preventing one child from ECMO cannulation was sufficient justification to halt the trial early and recruitment ceased on May 2, 1996. There were no significant differences between the study groups in the characteristics of the patients, treatment methods, or status at the time of randomization. The primary outcome of ECMO/death was lower in the iNO group 46% versus 64%; RR = 0.72; CI 95% 0.57-0.91 ($P = .006$). There was no difference in death between the 2 groups, the improved primary outcome coming from a reduced need for ECMO in the iNO treated patients 39% versus 55% ($P = .014$). There were no significant differences in toxicities between the 2 groups.

Study gas was not discontinued in any infant for toxicity; however, 11 patients in the iNO group required weaning of iNO concentration due to methemoglobin levels of 5% to 10%.

Although not designed to directly compare a dose response between 20 ppm and 80 ppm, the majority of patients in the NINOS trial responded to 20 ppm of iNO. Of the patients tried at 80 ppm, only a small percentage experienced added benefit; however, they experienced higher methemoglobin levels. Although targeted to enroll patients with oxygenation indexes within the (25-40) range, the population randomized experienced a mean oxygenation index of 46; providing a population with a much higher risk of ECMO or death than originally designed.

Planned post hoc analyses provided additional insights into clinical iNO therapy. As anticipated, patients with echocardiographic evidence of pulmonary hypertension experienced the greatest reduction in primary outcome, but even their counterparts without echocardiographic evidence of pulmonary hypertension experienced improved oxygenation. Also as anticipated, patients with the primary diagnosis of PPHN experienced the greatest reduction in primary outcome. However, the beneficial effect of iNO was not limited to this subgroup as the entire cohort (all primary diagnoses) experienced improved oxygenation with several demonstrating trends of reduced primary outcome as well. Three years later, the Clinical Inhaled Nitric Oxide Research Group confirmed these observations.

The NINOS trial was the first controlled clinical trial demonstrating that iNO therapy reduced the need for ECMO in neonates with hypoxic respiratory failure without significant toxicity. It demonstrated that regardless of echocardiographic evidence of pulmonary hypertension, iNO therapy could improve oxygenation in neonates with severe hypoxic respiratory failure. The multiple dosing strategy suggested that a dose of 80 ppm provided little benefit over 20 ppm but raised the potential for toxicity. The observation that patients in the lowest severity of illness subgroup (OI: 25.0-29.9) experienced a better oxygenation response and reduction in primary outcome with iNO therapy generated the hypothesis for the “Early iNO” study. The results of the NINOS trial, including the neuro-
developmental follow-up of NINOS participants (see below) proved to be essential to the FDA’s approval of iNO therapy.

**Inhaled Nitric Oxide and Hypoxic Respiratory Failure in Infants With Congenital Diaphragmatic Hernia**

The study design and primary hypothesis for this trial were the same as NINOS; however, the study population was limited to patients with CDH. Recruitment ceased when the main trial was terminated on May 2, 1996. With an enrollment of 53 patients, this study represents the largest controlled clinical trial conducted in the CDH population. Similar to the NINOS cohort, the mean OI in the CDH group was in excess of 45. In this cohort of acutely ill patients with CDH, there was no early improvement in oxygenation and no difference in the primary outcome between the iNO and control group (96% v 82%).27 More patients treated with iNO received ECMO 80% versus 54%, \( P = .043 \). The only appreciated benefit of iNO therapy in this patient population was short-term stabilization for transport or ECMO cannulation. Despite having little impact pre-ECMO, several patients were observed to have improved oxygenation when treated with iNO following ECMO therapy.

**Inhaled Nitric Oxide in Term and Near-term Infants: Neurodevelopmental Follow-up of the Neonatal Inhaled Nitric Oxide Study Group**

Follow-up is a critical component of treatment evaluation when introducing a new treatment into the neonatal population. Of the 199 surviving infants from the NINOS trial, 86.9% were seen in follow-up at 18-24 months of age. Complete history, physical and neurodevelopmental examinations were performed, including assessments of mental and motor development as measured by the Bayley Scales of Infant Development 2nd Edition29 and of hearing. Of the infants seen at follow-up, 32% presented with one or more neurodevelopmental disabilities (either cerebral palsy, mental developmental index (MDI) <70, psychomotor developmental index (PDI) <70, blind or hearing impaired).28 Eleven percent had cerebral palsy, 2% were blind (in one or both eyes), 30% experienced hearing impairment, 23% had a MDI <70 and 18% had a PDI <70. The only significant difference between the control group and iNO treated children was the incidence of seizures following discharge, occurring in 14.9% of control children and 4.7% of iNO treated children \( P = .046 \).

In the CDH parallel trial there were no significant differences in neurodevelopmental outcome among the 29 surviving infants. However, they also experienced a high rate of sensory neural hearing loss, 59% of controls and 43% in the iNO group. There were no significant differences in outcome among the infants who did not receive ECMO versus those who did, in either the main or CDH trials.

**Changes in Arterial Oxygen Tension When Weaning Neonates From Inhaled Nitric Oxide**

An ancillary investigation of the NINOS trial analyzed prospectively collected data during weaning of study gas. The objective of this observational study was to provide the clinician with anticipatory guidance when weaning iNO from a responding patient. Data from 505 weaning attempts recorded from 84 patients with varying diagnoses were analyzed. Ventilator settings and FiO\(_2\) had been maintained constant over a 30-minute period in which the response to weaning iNO was measured. Weaning intervals were every 12 hours when the iNO concentration was \( \leq 20 \) ppm. For patients requiring \( >20 \) ppm, weaning was attempted every 2 hours within the first 12 hours of therapy or until the iNO concentration reached 20 ppm. Weaning commenced when the clinician deemed the patient stable and the PaO\(_2\) was greater than 50 torr according to the following paradigm: \( 80 \rightarrow 40 \rightarrow 20 \rightarrow 10 \rightarrow 5 \rightarrow 0 \) ppm. Patients who failed weaning from 5 \( \rightarrow 0 \) ppm twice were weaned sequentially: \( 5 \rightarrow 4 \rightarrow 3 \rightarrow 2 \rightarrow 1 \rightarrow 0 \) ppm. Patient characteristics, prior treatments along with pre-wean variables were examined for relationships to the weaning response to iNO.

The vast majority (78%) of iNO weaning attempts were successful and well tolerated.30 Despite this, 13% of the patients subsequently required ECMO secondary to a progression of their symptoms. A reduction in PaO\(_2\) was observed at each weaning attempt when iNO was...
the NINOS study was dependent upon the FiO₂. Among discontinuation attempts, patients achieved better success discontinuing from 1 ppm than 5 ppm; odds ratio 4.4 (CI 95%: 1.9-10.4). Despite the improved success discontinuing from 1 ppm, several patients experienced repeated failures, prompting future Network iNO weaning guidelines to include reductions to 0.5 ppm prior to discontinuing iNO therapy.

Three variables were identified using a forward stepwise multiple regression analysis that accounted for 26% of the variability associated with the decline in PaO₂ when weaning iNO. These were the specific dose reduction, the pre-wean PaO₂ and surfactant treatment. With the greatest declines in PaO₂ occurring during iNO discontinuation, it is no surprise that the 1 → 0 ppm and 5 → 0 ppm iNO weans contributed significantly to the decline in PaO₂. When weaning iNO, the greater the pre-wean PaO₂ the greater the decline in PaO₂. Finally, patients treated with surfactant therapy experienced less decline in PaO₂ when weaning iNO, suggesting a synergistic effect between the therapies in this patient population.

The definition of a successful iNO wean for the NINOS study was dependent upon the FiO₂ and iNO concentration. For infants requiring a FiO₂ ≥ 0.50 on ≥20 ppm iNO, a weaning attempt was successful if the PaO₂ fell by no more than 25% and remained greater than 50 torr. For infants with a FiO₂ less than 0.50 or iNO greater than 20 ppm, a weaning attempt was considered successful if either the postductal saturation remained greater than 92% or the PaO₂ fell by no more than 50% from the baseline ABG and remained greater than 50 torr. The objective of these initial weaning definitions was to expedite weaning of the iNO concentration to 20 ppm or less and to tolerate wider fluctuations in PaO₂ in the more stable infants requiring lower FiO₂.

Because of the high success rate observed using these iNO weaning criteria and the demonstrated safety of iNO therapy at concentrations of ≥20 ppm, the Network modified the definition for a successful iNO wean for future investigations. When weaning iNO, the fall in PaO₂ is strongly dependent on the pre-wean PaO₂. Therefore an iNO weaning attempt is considered successful for pre-wean PaO₂ <100 torr: if the PaO₂ falls by no more than 20% and remains >60 torr and for pre-wean PaO₂ ≥100 torr: if the PaO₂ falls by less than 35% and remains >60 torr. These modified criteria appear to reduce some of the wide fluctuations in PaO₂ when weaning iNO, and provide a better oxygenation reserve with only a nominal increase (6%) in unsuccessful iNO weaning attempts.

A Randomized Trial of Early Versus Standard Inhaled Nitric Oxide Therapy in Term and Near Term Newborn Infants With Hypoxic Respiratory Failure

Although iNO therapy reduced the need for ECMO in several large randomized clinical trials, a significant number of infants continue to require ECMO or die. The NINOS subgroup analysis suggested that patients with the lowest severity of illness (OI: 25.0-29.9) experienced the best response and outcome to iNO therapy. We hypothesized that introducing iNO therapy earlier in the disease process, before significant alveolar atelectasis or ventilator-induced lung injury occurred, would further enhance the efficacy of iNO therapy.

The Early iNO Trial was developed as a sequential clinical trial evaluating iNO therapy in a less acute patient population. Surveillance of open label iNO use after the NINOS trial’s conclusion revealed that ~35% of infants who achieved 2 OI’s between (15 < 25) progressed to require ECMO or died. The Early iNO trial targeted this group of less severely ill infants. Patients were randomized to early iNO intervention versus control (simulation of iNO delivery). All patients received iNO therapy after achieving 2 consecutive OI’s ≥25 (standard therapy). The primary hypothesis of the trial was that early iNO would reduce the incidence of ECMO or death from 35% to 20%. To show this, a sample population of 400 infants was sought.

Unfortunately, the study was stopped in May 2001 after 3 years because of progressively declining enrollment. The baseline characteristics of the early-intervention group (n = 150) and control group (n = 149) were similar. The early iNO group experienced an improvement in oxygenation with 73% of patients experiencing a >20 torr increase in PaO₂ versus 37% of control
infants, \((P < .001)\). Despite the significant increase in oxygenation, the occurrence of ECMO, death or their combination was similar between the 2 groups, about 20\%. The control group progressed to standard iNO therapy and exceeded an OI \(\geq 40\) with greater frequency than the early iNO group signifying a greater progression of their respiratory failure. The benefit of improving oxygenation in this patient population remains undetermined; the neurodevelopmental follow-up of these patients is in progress.

**Inhaled Nitric Oxide for Preterm Infants With Severe Respiratory Failure**

Severe respiratory failure in the preterm infant is primarily a result of surfactant deficiency. Although surfactant therapy dramatically improves oxygenation, up to 50% of premature infants have a suboptimal response. Elevated pulmonary pressures with right-to-left shunting frequently complicates severe respiratory distress syndrome and is predictive of a poor outcome.

The initial reports of iNO use in preterm infants suggested an improvement in oxygenation, but the coincidental high incidence of intraventricular hemorrhage raised concerns. Since those initial reports, 2 randomized controlled clinical trials were conducted including a total experience of 168 preterm infants. Kinsella et al observed an improvement in oxygenation with iNO after 60 minutes, a reduced number of ventilator days and a lower incidence of chronic lung disease. The Franco-Belgium Collaborative Trial Group did not observe any significant difference in oxygenation or other outcomes in their premature population. Neither trial observed an increase of intraventricular hemorrhage in the iNO groups.

The question, “Can iNO therapy impact the management of severe respiratory failure in the preterm infant without causing toxicity,” remains unanswered. The Network is currently addressing this question. A randomized, controlled clinical trial is testing the primary hypothesis that the administration of iNO to premature infants weighing 401 to 1500 g with severe respiratory failure during the first 72 hours of life will reduce the incidence of death prior to discharge or bronchopulmonary dysplasia when compared to the control group by 20\%. The incidence and severity of intraventricular hemorrhage will also be closely monitored and neurodevelopmental testing will be performed on all study infants at about 18 months corrected age. Patient recruitment began in January 2001; with a planned study population of 440 infants, patient enrollment should be completed in late 2003.

**Conclusion**

These investigations culminate almost a decade of investigation by the NICHD Network in neonatal hypoxic respiratory failure and iNO therapy. The PPHN observational investigation described the epidemiology, outcomes and practice variations in neonates with PPHN, and examined our pre-iNO therapy approach to this patient population. This provided a foundation from which to build further inquiry into the management of this disease process. Resolving the uncertainty of NO\(_2\) kinetics within the respiratory circuit during iNO therapy clarified the potential for NO\(_2\) toxicity and paved the way for larger scale clinical investigations. The NINOS trial, including the neurodevelopmental component, provided the initial data demonstrating the safety and efficacy of iNO therapy for severe hypoxic respiratory failure. However, the follow-up study revealed that survivors of severe hypoxic respiratory failure experience significant morbidities regardless of the rescue therapies utilized (iNO, ECMO, neither). Recommendations regarding iNO treatment from the NINOS trial, including the weaning observations, have been incorporated into the design of the Early iNO trial, the Preterm iNO trial and into iNO clinical practice guidelines.

The neurodevelopmental follow-up of the Early iNO trial is near completion and should provide important safety information about iNO therapy in this population. The role of iNO therapy in the preterm infant continues to be investigated with the Preterm iNO trial. Overall, the Network’s randomized, controlled clinical investigations of iNO therapy including the planned neurodevelopmental follow-up component, set a high standard for the introduction and evaluation of new therapies for neonatal hypoxic respiratory failure. In addition to establishing efficacy and evaluating for toxicity, these investigations have broadened our understanding of the clinical management of this disease process.
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