Early Inhaled Nitric Oxide Therapy for Term and Near-Term Newborn Infants with Hypoxic Respiratory Failure: Neurodevelopmental Follow-Up

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Objective To report the neurodevelopmental outcome of infants enrolled in a randomized multicenter trial of early inhaled nitric oxide (iNO) in term and near-term neonates with hypoxic respiratory failure and pulmonary hypertension.

Study design Neonates born at ≥34 weeks gestation who required assisted ventilation and had an oxygenation index ≥15 and <25 were randomized to an early iNO group or a control group. A comprehensive neurodevelopmental assessment of survivors was performed at age 18 to 24 months.

Results The trial enrolled 299 infants, of which 266 (89%) survived to age 18 to 24 months (136 in the early iNO group and 130 in the control group). Follow-up evaluations were done on 234 (88%) of surviving infants. There were no differences between the 2 groups in the incidence of neurodevelopmental impairment (early iNO, 27%; control, 25%) and hearing impairment (early iNO, 23%; control, 24%). Mental development index scores were similar in the 2 groups; however, psychomotor developmental index scores were significantly higher in the control group (early iNO, 89 ± 17.7; control, 93.5 ± 18.4).

Conclusions Early iNO therapy for hypoxic respiratory failure in term and near-term infants is not associated with an increase in neurodevelopmental impairment or hearing loss at 18 to 24 months postnatal age. *(J Pediatr 2007;150:235-40)*

Inhaled nitric oxide (iNO) therapy reduces the use of extracorporeal membrane oxygenation (ECMO) in term and near-term infants with hypoxic respiratory failure.[1-4] Based on initial randomized clinical trials, iNO therapy is commonly used to treat moderate to severe neonatal respiratory failure with an oxygenation index (OI) ≥ 25.[5] A review of the previous randomized trials[1-4] showed that initiation of iNO therapy at a lower OI is associated with lower ECMO use/mortality. Consequently, we conducted a randomized, multicenter clinical trial of early initiation of iNO therapy for infants presenting with respiratory failure at an OI of 15 to 25 over a 3-year period from July 1998 to May 2001. The primary hypothesis for this study was that initiating iNO at an OI of 15 to 25 compared with use of standard iNO therapy at an OI ≥ 25 would decrease the rate of ECMO/mortality from 35% to 20%. A secondary hypothesis for this study was that early iNO therapy would not increase neurodevelopmental impairment or hearing loss rates among surviving infants at age 18 to 24 months compared with standard iNO therapy. Analysis of the outcomes observed before discharge from the hospital indicated that early iNO therapy did not reduce the combined incidence of ECMO/mortality and that individual ECMO and mortality rates were similar in the 2 groups. Early iNO therapy decreased the progression of respiratory failure to an OI > 25 and then to an OI > 40. Here we report the results of neurodevelopmental follow-up of the surviving infants at 18 to 24 months postnatal age.

CI	Confidence interval	MDI	Mental developmental index
CP	Cerebral palsy	OI	Oxygenation index
ECMO	Extracorporeal membrane oxygenation	PDI	Psychomotor developmental index
iNO	Inhaled nitric oxide		

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METHODS

The study was a prospective, randomized, double-masked clinical trial conducted in tertiary care neonatal intensive care units in the United States and Canada. The full details of the trial methods were published previously.[6]

Patient Population

Any infant delivered at ≥34 weeks of gestation with hypoxic respiratory failure secondary to idiopathic pulmonary hypertension, respiratory distress syndrome, perinatal aspiration syndrome, pneumonia/sepsis, or suspected pulmonary hypoplasia was eligible for participation in the trial. Infants were enrolled if they required assisted ventilation with an OI ≥ 15 and < 25 and a fraction of inspired oxygen (FiO_2) ≥ 0.8 on any 2 arterial blood gas measurements in a 15-minute to 12-hour window.

Infants were excluded from the trial if they were >14 days of postnatal age, had life-threatening congenital malformations, structural heart disease other than patent ductus arteriosus or patent foramen ovale, congenital diaphragmatic hernia, or previous exposure to iNO therapy. Informed consent was obtained from parents/guardians before randomization, and all of the participating centers obtained approval for the study from the pertinent institutional review boards. The consent form included a plan to obtain detailed neurodevelopmental and hearing assessments at 18 to 24 months postnatal age for surviving infants in the study.

Randomization

Infants were stratified by the study center and were randomized to early iNO or to simulated initiation of early iNO. This was done by a central computer accessed by telephone according to a permuted block design developed and implemented by the data-coordination center.

Follow-Up Assessment

Surviving infants were scheduled to be seen at age 18 to 24 months for a complete history, physical examination, audiologic assessment, neurologic evaluation, and developmental testing using Bayley Scales of Infant Development.[7] Anthropometric measurements were obtained at the follow-up visit, and growth percentiles were plotted using National Center for Health Statistics data. Information about intervening medical problems and socioeconomic data were also collected at this time. The neurologic assessment and developmental evaluations were performed by certified examiners trained to reliability in the examination procedure and were masked to study group assignment. The neurologic evaluation was based on the Amiel-Tison neurologic assessment[8] and included an evaluation of tone, strength, reflexes, and posture. Cerebral palsy (CP) was defined as abnormal muscle tone in at least 1 extremity and abnormal control of movement and posture. CP was then classified as mild, moderate, or severe. Mild CP was defined as motor function that slightly interfered with but did not prevent age-appropriate motor activities. The mild CP group included children capable of nonfluent walking, asymmetric walking, or persistent toe-walking with tight Achilles tendons resulting from increased tone; these children did not require an assistive device for walking. Moderate CP was defined as impaired motor function interfering with age-appropriate motor activities and was associated with ambulation requiring an assistive device or no ambulation but the ability to sit independently or with support. Severe CP was marked by impaired function interfering with all age-appropriate motor activity to the point that the child was unable to ambulate or sit, even while supported. For developmental assessment, the Bayley Scales of Infant Development II[7] were administered; from this information, a mental developmental index (MDI) and a psychomotor developmental index (PDI) were derived.

A comprehensive audiologic assessment was done, including speech awareness in the sound field as well as bone conduction, warbled pure-tone thresholds in the sound field at 250 to 4000 Hz, and tympanometry. Responses were compared with previously established norms.[9] For the purpose of the study, normal hearing was defined as threshold responses to speech awareness in the sound field and pure-tone thresholds in the sound field at ≤40 decibels. The children were classified into 4 groups: normal hearing, sensorineural hearing loss, conductive loss, and undetermined. A diagnosis of blindness was based on an ophthalmologist report of uncorrectable vision ≤20/200 in the better eye. Neurodevelopmental impairment was defined as the presence of any of the following: moderate or severe CP, Bayley MDI < 70, Bayley PDI < 70, blindness, or permanent hearing impairment requiring amplification.

Statistical Analysis

Continuous variables were compared using *t*-tests or Wilcoxon's test for nonparametric data. Discrete variables were compared using χ^2 tests or Fisher's exact test as appropriate. A P value < .05 was considered significant. The 95% confidence intervals (CIs) for the differences between continuous and discrete variables were computed; a difference was considered statistically significant if the 95% CI for the difference did not include 0.[10]

RESULTS

A total of 299 infants were enrolled in the original trial (Table I); 30 infants died before discharge (13 in the early iNO group and 17 in the control group). Of the 269 infants who survived to discharge from the hospital, 3 additional infants died before reaching 18 to 24 months postnatal age (1 in the early iNO group and 2 in the control group). Of the remaining 266 infants, 234 (88%; 121 in the early iNO group and 113 in the control group) were seen for follow-up evaluation.

The neonatal characteristics, including birth weight, gestation, and sex distribution, did not differ between the 2 groups (Table I). Infants in both groups were evaluated at similar chronologic and adjusted postnatal ages (Table I).

Table I. Neonatal characteristics of the survivors of the early iNO trial evaluated at follow-up

	Early iNO group	Control group
Randomized at study entry, n	150	149
Age at study entry in hours, median (1st to 3rd quartile range)	28.5 (14-46)	24.8 (12-47)
Survived to discharge, n (%)	137 (91)	132 (89)
Survived to age 18 to 24 months, n (%)	136 (90.6)	130 (87.2)
Evaluated at age 18 to 24 months, n (%)	121 (88.9)	113 (86.9)
Birth weight, g	3320 ± 690	3345 ± 552
Gestational age, weeks	38.5 ± 1.9	38.8 ± 1.9
Female sex, n (%)	58 (48)	43 (38)
Chronological age, months	20.9 ± 2.9	20.8 ± 4.1
Adjusted age, months	20.7 ± 3.0	20.6 ± 4.1
Received standard iNO, n (%)*	46 (38)	57 (50)
Received ECMO, n (%)	12 (10)	12 (11)

*Infants in either group who progressed to an OI of 25 received standard iNO therapy.

Although all infants in the early iNO group had received iNO, standard iNO therapy, given at an OI of ≥ 25, was provided to 38% of the surviving infants in the early iNO group and to 50% of the surviving infants in the control group. The number of infants receiving ECMO support was similar in both groups. The 2 groups were similar in terms of ethnic distribution, maternal marital status, and maternal education (data not shown). Overall, 18% of the mothers completed 10 to 12 years of education, 30% had a high school diploma, and 23% attended college.

Information for postdischarge medication use and use of adaptive equipment was collected by a standardized parental questionnaire (Table II). At the time of follow-up evaluation, 35% of the infants in the study were rehospitalized at least once. This is similar to the 36% rehospitalization rate previously reported in the follow-up of cohort from the NINOS trial.[11] The most commonly used postdischarge medications included bronchodilators and home oxygen. There were no significant differences between the 2 groups in terms of any medical and community resource needs (Table II). No significant differences in growth measurements were noted between the 2 groups (data not shown). Approximately 20% of the study infants had weight below the 10th percentile, and 15% of the infants had length and head circumference below the 10th percentile.

Approximately 87% of the infants had normal neurologic assessment findings (84% of those in the early iNO group and 91% of those in the control group; Table III). The overall incidence of CP and the incidence of moderate to severe CP did not differ in the 2 groups. There was no difference in the rate of moderate to severe neurologic abnormalities between the 2 groups.

Developmental assessment with the Bayley Infant Development Scale showed no difference in MDI scores between the study groups. The percentage of infants with an MDI score < 70 was similar in the 2 groups. The PDI scores were significantly higher in the control group; however, the percentage of infants with a PDI score < 70 was similar in the 2 groups. Reanalyzing the data after excluding the 12 infants with moderate to severe CP did not significantly affect the trends in MDI and PDI in the 2 groups; the mean MDI score was 85.2 ± 19.9 in the early iNO group, compared with 87.9 ± 18.6 in the control group ($P = .26$). Approximately 21% of the infants in the early iNO group and 19% of those in the control group had an MDI score < 70. The PDI scores were 91.3 ± 15.3 for the early INO group and 95.7 ± 15.9 for the control group ($P = .006$). The percentage with a PDI score < 70 remained similar between the 2 groups, 6.8% in the early iNO group versus 7% in the control group ($P = .95$).

Overall, 203 of the 234 infants seen on follow-up examination underwent a complete audiologic assessment. There was no difference between the 2 groups in the percentage of assessed infants with normal findings or in the incidence of sensorineural or conductive hearing loss. The percentage of infants requiring tympanostomy tube placement was similar in the 2 groups (9.1% in the early iNO group vs 12.6% in the control group). There was no difference between the 2 groups in the incidence of unilateral or bilateral vision loss. We found that 72% of the infants in the early iNO group and 75% of those in the control group were free of neurodevelopmental impairments, including moderate or severe CP, Bayley MDI < 70, Bayley PDI < 70, blindness, or permanent hearing impairment requiring amplification.

Comparing the outcomes for the 46 infants in the early iNO group and 57 infants in the control group who progressed to standard iNO therapy at OI ≥ 25 demonstrated no differences between the 2 groups in terms of the percentage of infants with moderate to severe abnormalities on neurologic assessment. Infants who received standard iNO therapy in the 2 groups also had similar MDI and PDI scores, hearing loss rate, and rate of neurodevelopmental impairment (early iNO group, 34%; control group, 26%; $P = .36$). Comparing the data for 12 infants in each group who progressed to receive ECMO showed no differences between the 2 groups for these variables.

Exposure to any iNO therapy was not associated with increased neurodevelopmental impairment in the 178 infants who had iNO exposure compared to 56 control infants without iNO exposure. The MDI scores (84.1 ± 19.8 for iNO exposure vs 86.4 ± 22.4 for no iNO exposure; $P = .36$) and PDI scores (90.8 ± 17.2 for iNO exposure vs 92.6 ± 20.9 for no iNO exposure: $P = .13$) were similar for the 2 groups. Similarly, neurodevelopmental outcomes for the 24 infants who received ECMO support (MDI, 85.8 ± 23.9; PDI, 92.8 ± 15.3) were similar to those in the 211 infants without ECMO support (MDI, 84.5 ± 20 [$P = .66$]; PDI, 91 ± 18.5 [$P = .68$]). We performed secondary analyses of the data to identify any associations between neurodevelopmental im-

Table II. Health status outcomes for survivors of the early iNO trial

Variable	Early iNO (n = 121)	Control (n = 113)	*P* value	95% CI for the difference
Hospitalized since discharge, n (%)	43 (35.3)	41 (36.3)	.87*	−11.1, 13.3
Home medications, n (%)				
Bronchodilators	27 (22)	19 (17)	.29*	−15.7, 4.8
Diuretics	2 (1.6)	2 (1.8)	1.0†	−4.5, 4.8
Anticonvulsants	5 (4.1)	2 (1.8)	.45†	−7.9, 2.8
Tracheotomy, n (%)	2 (1.7)	0 (0)	.50†	−6.2, 1.8
Home oxygen, n (%)	14 (11.5)	6 (5.4)	.09*	−13.7, 1.2
Home ventilator, n (%)	3 (2.5)	0 (0)	.25†	−7.4, 0.9
Gastrostomy/tube feeding, n (%)	10 (8)	4 (4)	.14*	−11.4, 1.7
Use of adaptive equipment, n (%)	6 (5)	6 (5.5)	.89†	−6.3, 7.1
Stroller/wheelchair, n (%)	4 (3.4)	1 (0.9)	.37†	−7.7, 2.1
Braces/orthotics, n (%)	2 (1.7)	6 (5.5)	.16†	−1.2, 10.0
Walker, n (%)	0	2 (1.8)	.23†	−1.5, 6.8

*By the χ^2 test.
†By Fisher's exact test.

Table III. Neurodevelopmental impairments at age 18 to 24 months in the early iNO and control groups

Variable	Early iNO (n = 121)	Control (n = 113)	*P* value	95% CI for the difference
Cerebral palsy—all degrees, n (%)	10 (8.2)	7 (6.3)	.58*	−9.0, 5.3
Cerebral palsy—moderate to severe, n (%)	6 (4.9)	3 (2.7)	.50†	−8.2, 3.6
Any neurologic abnormality, n (%)	20 (16.4)	10 (9.2)	.10*	−16.0, 1.5
Moderate/severe neurologic abnormality, n (%)	6 (4.9)	3 (2.8)	.51†	−8.0, 3.5
Bayley MDI, mean/median (SD)	83.3/87 (21.0)	86.1/90 (19.9)	.28‡	−8.0, 2.0§
MDI < 70, n (%)	28 (25.2)	24 (22.9)	.68*	−13.7, 9.1
Bayley PDI, mean/median (SD)	89.0/93 (17.7)	93.5/98 (18.4)	.009‡	−9.0, −1.0§
PDI < 70, n (%)	13 (11.9)	12 (11.4)	.91*	−9.4, 8.5
Blindness, n (%)				
Unilateral	1 (0.8)	1 (0.9)	1.0†	−3.9, 4.4
Bilateral	4 (3.4)	1 (0.9)	0.37†	−7.7, 2.2
Hearing status, n (%)				
Normal hearing	79 (76.7)	76 (76)	.91*	−12.5, 11.0
Sensorineural loss	7 (6.8)	10 (10.0)	.41*	
Conductive loss	16 (15.5)	7 (7.0)	.055*	
Undetermined/other	1 (0.97)	7 (7.0)	.03†	
Hearing impairment requiring amplification	1 (1.0)	3 (3.0)	.37†	
Seizure disorder, n (%)	4 (3.4)	4 (3.7)	1.0†	
Hydrocephalus with shunt, n (%)	0 (0)	0 (0)		
Any neurodevelopmental impairment, n (%)	34 (27.9)	28 (24.6)	.56*	−14.5, 8.0

*By the χ^2 test.
†By Fisher's exact test.
‡By Wilcoxon's test.
§CIs are for difference in medians for these variables.

pairments and various adjunctive therapies used during the hospital stay that have been reported to be risk factors for such impairments.[12-17] The use of skeletal muscle relaxants (in 134 infants with iNO exposure and 95 infants without exposure) was not associated with increased neurodevelopmental or hearing impairments (data not shown). The 98 infants (43.7%) exposed to postnatal steroids during the hospital stay appeared to have a higher incidence of neurodevelopmental impairments (34.7%) than the infants who had no exposure (19.8%; $P < .01$). However, further analysis of the data revealed that those infants exposed to postnatal steroids were sicker and were more likely to have received volume expanders, vasopressor support, standard iNO therapy, high-frequency oscillation, and longer duration of ventilator support and had a higher incidence of chronic lung disease. A multiple logistic regression analysis model showed that steroid exposure is not an independent risk factor for adverse neurodevelopmental outcome; the odds ratio for neurodevelopmental impairments in the unexposed group was 0.51 with a 95% CI of 0.25 to 1.01 ($P = .053$).

DISCUSSION

The early introduction of iNO therapy for term and near-term infants with moderate respiratory failure (OI 15 to 25) improved oxygenation and decreased the progression to more severe respiratory failure.[6] However, early initiation of iNO therapy did not reduce the use of ECMO/mortality in this study. The study infants were followed prospectively to age 18 to 24 months to determine whether this intervention had any effect on long-term neurodevelopmental outcome. Although the study was not powered to detect a prespecified difference in neurodevelopmental outcome between these 2 groups, a secondary hypothesis of the study was that early iNO would not increase the incidence of neurodevelopmental impairments at age 18 to 24 months. Our data show that the early iNO and control groups did not differ significantly in terms of most long-term neurodevelopmental outcome variables. Although the proportion of infants with medical problems, such as the need for home medications, oxygen, and ventilator support and abnormal neurologic assessment findings, appears to be higher in the early iNO group, the 95% CIs show that these differences are not significant. The clinically significant neurodevelopmental impairments, such as moderate to severe CP, Bailey MDI and PDI scores < 70, blindness, and hearing loss, show equivalent outcomes with $P \geq 0.5$ and the 95% CI for difference distributed well on both sides of 0.

Three randomized trials of iNO therapy included neurodevelopmental follow-up at age 18 to 24 months.[11,18,19] In these studies, which included a placebo control group for comparison with iNO treatment, no differences in the neurodevelopmental impairments were noted between the control and treatment groups. The early iNO trial enrolled infants with less severe respiratory failure compared with the previous trial conducted by our group,[11] and in the present trial the overall incidence of abnormal neurologic findings was 12.8%, compared with 21.5% in our previous trial. The prevalence of moderate to severe CP was 3.8% in the present trial, compared with 7.6% in our previous trial.

Although our trial enrolled infants with less severe respiratory failure, we found a high use of supportive therapies, such as volume expanders and vasopressors (in >80%) and sedation and analgesia (in 96%).[6] In addition, >60% of the study infants received surfactant therapy, 44% received high-frequency ventilation, 56% underwent skeletal muscle paralysis, and 43% were given postnatal steroids. An association between the use of these therapies and an elevated incidence of neurodevelopmental impairments and hearing loss was suggested in previous follow-up studies.[12-17] In the present study we found no association between the use of skeletal muscle relaxants and postnatal steroids and neurodevelopmental impairments, in contrast to previous studies reporting worse long-term outcome with the these therapies.[12-17]

As part of the study protocol, we performed a complete audiologic assessment in the study infants. The overall incidence of hearing loss (24%) was similar to what we observed in the follow-up of infants in the NINOS trial.[11] Although we found no difference in the prevalence of hearing loss in the early iNO and control groups in our study, a relatively high incidence of hearing loss persisted in this cohort of less sick infants. Whether this high rate of hearing loss is related to respiratory failure or to the use of adjunctive therapies, such as alkalosis, analgesia, and neuromuscular blocking agents,[12-15] remains unknown.

Bayley MDI scores were similar in the 2 groups, but PDI scores differed. This difference in PDI scores persisted even after the exclusion of infants with moderate to severe CP. The MDI and PDI scores showed significant variability, with a standard deviation of 18 to 21 points. In addition, the data were subjected to multiple comparisons, which could increase the probability of a type 1 error[10] for the observed difference. However, a possible adverse effect of early iNO in term and near-term neonates with respiratory failure cannot be excluded. We observed lower PDI scores at the follow-up of the NINOS trial for the iNO group compared with the control group, though the difference was not statistically significant. Comparing the PDI scores for the infants who progressed to standard INO therapy in both treatment groups in the early iNO trial showed that the difference was not significant, indicating that early initiation of iNO therapy did not have an adverse effect on outcome in infants who experienced progressive respiratory failure. In addition, iNO therapy itself and ECMO support did not affect neurodevelopmental outcome. Note, however, that our samples of infants who did not receive iNO therapy (56 infants) and those who received ECMO support (24 infants) are small.

Our early iNO and control groups were similar in terms of all measured socioeconomic variables. The 2 groups had similar postdischarge medical needs, including rates of hospital readmission, need for home oxygen, tube feedings, and other medications. Therefore, the neurodevelopmental outcomes in our study subjects were unlikely to be influenced by differences in health status or socioeconomic factors.

In conclusion, our findings indicate that early iNO therapy was not associated with an increase in medical, neurodevelopmental, or hearing abnormalities at age 18 to 24 months compared with standard iNO therapy in a population of term or near-term infants with hypoxic respiratory failure. Even though early iNO therapy decreased the progression of respiratory failure in these infants, this apparent benefit was not associated with a decrease in long-term morbidity. Survivors of neonatal hypoxic respiratory failure remain at a significant risk for neurodevelopmental and hearing deficits and need close monitoring and follow-up. Whether these abnormalities are related to underlying disease process or to the postnatal interventions used in these infants remains unknown and requires further investigation.

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APPENDIX

The Neonatal Inhaled Nitric Oxide Study was a collaboration of the National Institute of Child and Health and Human Development Neonatal Research Network and the Canadian Inhaled Nitric Oxide Study Group. The following institutions and investigators participated in the trial. Members of the Executive Committee are indicated by asterisks.

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