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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Supported by the National Institute of Child and Health and Human Development Neonatal Research Network (grants U10 HD21397, U10 HD40689, U10 HD21385, U10 HD21415, U10 HD21397, U10 HD27881, M01 RR00997, U10 HD27853, M01 RR08084, U10 HD27856, M01RR00750, U10 HD27871, M01RR06022, U10 HD27904, U10 HD27880, M01 RR00070, U10 HD34216, U10 HD34167, M01 RR02635, M01 RR02172, M01RR01032, and U10 HD21373) and the Canadian Institute of Health Research (grant UI 15246). Study gas and delivery devices were provided by INO Therapeutics Inc, Clinton, NJ.

Submitted for publication Apr 5, 2006; last revision received Oct 5, 2006; accepted Nov 30, 2006.

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0022-3476/$ - see front matter

10.1016/j.jpeds.2006.11.065

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).