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

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Abstract

Objective—To report the neurodevelopmental outcome of infants enrolled in a randomized multi-center 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 were randomized to early iNO or control group if they required assisted ventilation and had an oxygenation index (OI) ≥ 15 and < 25 . A comprehensive neuro-developmental assessment of survivors was performed at 18–24 months of age.

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

Conclusion—Early iNO therapy for hypoxic respiratory failure in term and near term infants is not associated with an increase in neuro-developmental impairments or hearing loss at 18–24 months postnatal age.

Keywords

nitric oxide therapy; pulmonary hypertension; neuro-developmental outcome

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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 the initial randomized clinical trials, iNO therapy is commonly used for treating moderate to severe neonatal respiratory failure with an oxygenation index (OI) ≥ 25 (5). A review of the previous randomized trials (1–4) indicated that initiation of iNO therapy at a lower oxygenation index was associated with lower ECMO use/mortality. Therefore, we conducted a randomized, multi-center clinical trial of early initiation of iNO therapy for babies presenting with respiratory failure at an oxygenation index of 15–25 over a three-year period from July 1998 – May 2001. The primary hypothesis for this study was that initiation of iNO at an oxygenation index of 15–25 compared to use of standard iNO therapy at an oxygenation index ≥ 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 18–24 months of age compared to use of standard iNO therapy. Analysis of the outcomes observed prior to discharge from the hospital indicated that early iNO therapy did not reduce the combined incidence of ECMO/mortality and the rates of ECMO and mortality individually were similar between the groups. Early iNO therapy decreased the progression of respiratory failure to an oxygenation index >25 and to an oxygenation index >40 . Here we report the results of the neurodevelopmental follow-up of the surviving infants at 18–24 months of postnatal age.

Methods

The study was a prospective, randomized, double masked clinical trial conducted in tertiary care neonatal intensive care units in USA 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. Babies were enrolled if they required assisted ventilation with an oxygenation index ≥ 15 and <25 and an $\text{FiO}_2 \geq 0.8$ on any two arterial blood gases in a fifteen minute to twelve 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 prior exposure to iNO therapy. Informed consent was obtained from parents/guardians before randomization and all the participating centers obtained approval for the study from institutional review boards. The consent form included a plan to obtain detailed neurodevelopmental and hearing assessments at 18–24 months of 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-coordinating center.

Follow-up assessment

Surviving infants were scheduled to be seen at 18–24 months for a complete history, physical exam, 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 NCHS data. Information about intervening

medical problems and socioeconomic data were also collected. The neurologic assessment and developmental evaluations were performed by certified examiners who were 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 was defined as abnormal muscle tone in at least one extremity and abnormal control of movement and posture. Cerebral palsy was then classified as mild, moderate, or severe. Mild cerebral palsy was motor function that interfered slightly with, but did not prevent age appropriate motor activities. Mild cerebral palsy group included babies that are capable of non-fluent walking, asymmetric walking, or persistent toe walking with tight Achilles tendon resulting from increased tone; these children did not require an assistive device for walking. Moderate cerebral palsy was defined as impairment of motor function that interferes with age appropriate motor activities and was associated with ambulation requiring an assistive device or no ambulation; but the child can sit independently or sit with support. Severe cerebral palsy group included children with impairment of function interfering with all age appropriate motor activity to the point that the child was unable to ambulate, sit or have supported sitting. For developmental assessment, the Bayley Scales of Infant Development II (7) were administered and from this information, a mental developmental index (MDI) and psychomotor developmental index (PDI) were derived. A comprehensive audiologic assessment was done including speech awareness in sound field as well as by bone conduction, warbled pure tone thresholds in sound field at 250 to 4,000 Hz and tympanometry. Responses were compared to previously established norms (9). For the purpose of the study, normal hearing was defined as threshold responses to speech awareness in sound field and pure tone thresholds in sound field at ≤ 40 decibels. Children were classified into four groups: normal hearing, sensory-neural hearing loss, conductive loss, or undetermined. A diagnosis of blindness was based on an ophthalmologist report of uncorrectable vision $\leq 20/200$ in the better eye. Neuro-developmental 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 tests for nonparametric data. Discrete variables were compared using Chi-Square tests or by Fisher Exact Test as appropriate. A p value of < 0.05 was considered significant. 95% confidence intervals 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 including 13 in the early iNO group and 17 in the control group. Of the 269 infants that survived to discharge from the hospital, 3 additional infants died prior to reaching 18 to 24 months of postnatal age (one in the early iNO group and two in the control group). Of the remaining 266 infants, 234 infants (88%) were seen for follow-up evaluation. This included 121 infants in the early iNO group and 113 infants in the control group.

The neonatal characteristics, including birth weight, gestation, and sex distribution did not differ between groups (Table I). Infants in both groups were evaluated at similar chronologic and adjusted postnatal age (Table I). 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 who received ECMO support was similar in both groups. The two groups were similar for 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 post discharge 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 babies in the study were re-hospitalized at least one time. This is similar to 36% re-hospitalization rate previously reported in the follow-up of cohort from NINOS trial (11). Post discharge medications most commonly used included bronchodilators and home oxygen. There were no significant differences between the two groups for any of the medical and community resource needs (Table II). No significant differences in growth measurements were noted between the two groups (data not shown). Approximately 20% of the study infants had weight <10 percentile and 15% of the infants had length and head circumference < 10 percentile.

Approximately 87% of the infants were found to be normal by neurological assessment (Table III). The overall incidence of cerebral palsy and the incidence of moderate to severe cerebral palsy were not different between the two groups. Overall, a normal neurological exam was observed in 84% of the infants in the early iNO group and 91% of the control group of infants. There was no difference between the two groups in the incidence of moderate to severe neurological abnormalities between the two groups.

The developmental assessment with the Bayley Infant Development Scale showed no differences in scores for MDI between the groups. The percent of babies scoring at an MDI <70 were similar between the two groups. The psychomotor developmental index scores (PDI) were significantly higher in the control group. The percent of babies scoring <70 on PDI were similar between the two groups. Reanalyzing the data after excluding the 12 infants with moderate to severe cerebral palsy did not significantly influence the trends in MDI and PDI between the two groups. After the exclusion of 12 infants with moderate to severe cerebral palsy, infants in the early iNO group had mean MDI scores of 85.2 ± 19.9 compared to control group scores of 87.9 ± 18.6 (p value 0.26). Approximately 21% of the infants in the early iNO group and 19% of the infants in the control group had MDI <70, after the exclusion of these 12 infants. The PDI scores were 91.3 ± 15.3 for the early iNO group and 95.7 ± 15.9 for the control group (p value = 0.006). The percent with PDI <70 remained similar between the two groups, 6.8% early iNO versus 7% control group (p value = 0.95).

Overall, 203 of the 234 infants seen at the follow-up examination had a complete audiological assessment. There was no difference between the two groups for the percent of assessed infants having normal exams. There was no difference between the two groups in the incidence of sensori-neural or conductive hearing loss. The number of babies requiring tympanostomy tube placement were similar between the two groups (9.1% early iNO group, compared to 12.6% in the control group). There was no difference between the two groups in the incidence of unilateral or bilateral vision loss. We found that 72% of the early iNO group and 75% of the control group were free of any neuro-developmental impairments (NDI- moderate or severe cerebral palsy, Bayley MDI < 70, Bayley PDI < 70, blindness, or permanent hearing impairment requiring amplification).

A comparison of the outcomes for the 46 infants in the early iNO group and 57 infants in the control group that progressed to standard iNO therapy at $OI \geq 25$ demonstrated no differences between the two groups for the percent of infants that had moderate to severe abnormality on neurological assessment. Infants who received standard iNO therapy in the two groups also had similar MDI and PDI scores, hearing loss rates and occurrence of any neurodevelopmental impairment (early iNO group 34% and the control group 26%, $P = 0.36$). Comparison of the data for 12 infants in each group who progressed to receive ECMO also did not demonstrate differences between the two groups for these variables.

Exposure to any iNO therapy was not associated with increased neurodevelopmental impairments in the 178 infants that had exposure compared to 56 control infants that never had iNO exposure. The MDI scores (84.1 ± 19.8 for iNO exposed and 86.4 ± 22.4 for babies that had no iNO exposure, $P=0.36$) and PDI scores (90.8 ± 17.2 for iNO exposed and 92.6 ± 20.9 for babies with no iNO exposure, $P=0.13$) were similar for the two groups. Similarly neuro-developmental outcome for the 24 infants that received ECMO support (MDI 85.8 ± 23.9 and PDI 92.8 ± 15.3) was similar to the 211 infants without ECMO support (MDI 84.5 ± 20 , $P=0.66$ and PDI 91 ± 18.5 , $P=0.68$). We performed secondary analyses of the data to identify association of neuro-developmental impairments with some adjunctive therapies used during the hospital stay that were previously reported to be risk factors for such impairments (12–17). The use of skeletal muscle relaxants (134 infants with exposure and 95 infants without exposure) was not associated with increased neuro-developmental or hearing impairments (data not shown). The 98 infants (43.7%) exposed to postnatal steroids during hospital stay appeared to have a higher incidence of neuro-developmental impairments (34.7%) than infants that had no exposure (19.8%, $p<0.01$). However, further analysis of the data revealed that infants exposed to postnatal steroids were sicker and were more likely to have received volume expanders, vasopressor support, standard iNO therapy and high frequency oscillation, longer duration of ventilator support and had a higher incidence of chronic lung disease. Multiple Logistic regression analysis model showed that steroid exposure is not an independent risk factor for adverse neuro-developmental outcome; odds ratio for neuro-developmental impairments in the unexposed group was 0.51 with 95% confidence intervals of 0.25–1.01 ($P=0.053$).

Discussion

The early introduction of iNO therapy for term and near-term infants with a moderate degree of respiratory failure (OI =15–25) improved the 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 18–24 months of age to determine if this intervention had any effect on the long-term neurodevelopmental outcome for these infants. Although the study was not powered to detect a pre-specified difference in the neurodevelopmental outcome between these two groups, one of the secondary hypotheses of the study was that early iNO would not increase the incidence of neurodevelopmental abnormalities at 18–24 months of age. Our data show that early iNO and control groups did not differ significantly in the majority of long-term neuro-developmental outcome variables. Although the proportion of babies with medical problems such as the need for home medications, oxygen and ventilator support and abnormal neurological assessment appear higher in the early iNO group, 95% CI show that these differences are not significant. The clinically significant neuro-developmental impairments, such as moderate to severe CP, Bailey MDI and PDI < 70, blindness and hearing loss show equivalent outcomes with p Values ≥ 0.5 and 95% CI for difference distributed well on both sides of 0.

Three randomized trials of iNO therapy included neurodevelopmental follow-up at 18–24 months of age (11,18,19). In these studies, which included a placebo control group for comparison to iNO, no differences in the neurodevelopmental impairments were noted between the control and treatment groups. The early iNO trial enrolled babies with less severe respiratory failure than the previous trial done by our group (11), and the overall incidence of abnormal neurological exam is 12.8% in this trial compared to 21.5% in our previous trial. Moderate - severe cerebral palsy was noted in 3.8% in this trial compared to 7.6% in our previous trial.

Although our trial enrolled babies with less severe respiratory failure, we observed a high prevalence of the use of supportive therapies such as volume expanders and vasopressors,

which were used in over 80% and sedation and analgesia, which were used in 96% of the study infants. (6) In addition, over 60% of the study infants received surfactant therapy and 44% of the infants were tried on high frequency ventilation. Skeletal muscle paralysis was used in 56% of infants. Postnatal steroids were given to 43% of study infants. An association between the use of these therapies and a higher incidence of neurodevelopmental abnormalities and hearing loss was suggested in previous follow-up studies (12–17). We found that the use of skeletal muscle relaxants and postnatal steroids was not associated with neuro-developmental impairments in this study in contrast to the previous studies that reported worse long term outcome with the use of 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 at the follow-up of infants in the NINOS trial (10). Although there was no difference in the incidence of hearing loss between 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 hearing loss rate is related to the respiratory failure or the use of adjunctive therapies, such as alkalosis, analgesia and neuromuscular blocking agents (12–15) remains unknown.

We found that the MDI scores from the Bayley assessment were similar between the two groups. However, the two groups differed with respect to their scores on the PDI. This difference in the score persisted even after exclusion of babies that were noted to have moderate to severe cerebral palsy. The MDI and PDI scores showed significant variability with a standard deviation of 18–21 points. In addition, the data were subjected to multiple comparisons that may 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 can not be excluded from our study. We observed lower PDI scores at the follow-up of the NINOS trial for the iNO group compared to control group, though the difference was not statistically significant. When we compared the PDI scores for babies that progressed to standard INO therapy in both treatment groups in the early iNO trial, the difference in the PDI scores was not significant. Therefore, early initiation of iNO therapy did not have an adverse effect on the outcome for babies that had progression of their respiratory failure. In addition, iNO therapy itself or ECMO support did not affect the neurodevelopmental outcome compared to infants that did not receive these therapies. However, our sample sizes for babies that did not receive iNO therapy (56 infants) and babies that received ECMO support (24) are small.

Our early iNO and control groups were similar for all measured socioeconomic variables. The two groups experienced similar post-discharge 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, early iNO therapy was not associated with an increase in medical, neurodevelopmental, or hearing abnormalities at 18–24 months of age compared to standard use of 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 of neurodevelopmental and hearing deficits and require 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 NICHD 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.) **NINOS Follow-Up Principal investigators:** *Case Western Reserve University, Cleveland* – D. Wilson; *University of Texas, Dallas* -- S. Broyles; *Wayne State University, Detroit* – V.D. Black; *University of Toronto, Toronto* – A. James; *University of Tennessee, Memphis* – K. Yolton; *University of Miami, Miami* – C. Bauer; *University of New Mexico, Albuquerque* – G. Laadt; *University of Cincinnati, Cincinnati* – J. Steichen; *Indiana University, Indianapolis* – A. Dusick; *Yale University, New Haven* – L. Mayes; *Women and Infants' Hospital, Providence* – B. Vohr; *Stanford University, Palo Alto* – B. Fleisher; *University of Alabama, Birmingham* – K. Nelson; *Harvard University, Boston* – K. Lee; *University of Texas, Houston* – B. Morris; *University of Alberta, Edmonton* – C. Robertson; *University of Calgary, Calgary* – R. Sauve; *University of British Columbia, Vancouver* – M. Whitfield; *Baylor College of Medicine, Houston* – A. Reynolds; *McGill University, Montreal* – P. Riley; *University of Ottawa, Ottawa* – M. Blayney; *McMaster University, Hamilton* – S. Saigal; *University of Manitoba, Winnipeg* – O. Casiro. **NICHD Neonatal Research Network:** *Case Western Reserve University, Cleveland* -- *E. Stork, A.A. Fanaroff, E. Gorjanc; *University of Texas, Dallas* -- A.R. Laptook, S. Madison; *Wayne State University, Detroit* -- S. Shankaran, R. Bara, G. Muran; *University of Tennessee, Memphis* -- S.B. Korones, T. Hudson; *University of Miami, Miami* -- S. Duara, C.R. Bauer, R. Everett; *University of New Mexico, Albuquerque* -- M. Crowley, L-A. Papile, C. Backstrom; *University of Cincinnati, Cincinnati* -- J. Fridriksson, E.F. Donovan, M. Mersman; *Indiana University, Indianapolis* -- *G.M. Sokol, J.A. Lemons, D. Appel; *Yale University, New Haven* -- *R.A. Ehrenkranz, P. Gettner; *Women and Infants' Hospital, Providence* -- W. Oh, A. Hensman; *Stanford University, Palo Alto* -- *K.P. Van Meurs, D.K. Stevenson, M.B. Ball; *University of Alabama, Birmingham* -- W.A. Carlo, S. Cosby; *Harvard University, Boston* -- E. Eichenwald, A.R. Stark, K. Fournier; *University of Texas, Houston* -- K. Kennedy, J.E. Tyson, G. McDavid; *Medical College of Wisconsin, Milwaukee* -- *G. Konduri, P. Hamm. **Canadian Inhaled Nitric Oxide Study Group:** *University of Alberta, Edmonton* -- *A. Peliowski, B. Young; *University of Calgary, Calgary* -- *N. Singhal, L. Bourcier; *University of British Columbia, Vancouver* -- *A. Solimano, F. Germain, A. J. Singh; *Baylor College of Medicine, Houston* -- M. Wearden, C. Fernandes, S. Hegemier; *University of Manitoba, Winnipeg* – R. Alvaro, N. Johnston; *McGill University, Montreal* -- R. Gosselin, K. Mullahoo; *McMaster University, Hamilton* -- *H. Kirpalani, S. Monkman; *University of Ottawa, Ottawa* -- *R. Walker, L. Ramnarine; *University of Toronto, Toronto* -- A. James, M. Finelli; *St Joseph's Hospital, Phoenix* -- Carlos Fajardo, E. Ramthun; *Children's Hospital and Health Center, San Diego* -- G. Knight; *University of Washington, Seattle* -- D. Mayock, S. Jacques; *Phoenix Children's Hospital Phoenix* -- Daniel Sprague, J. Andrews. **Data Safety and Monitoring Committee:** *Children's Hospital National Medical Center, Washington DC* – G. Avery (Chairman); *New England Medical Center, Boston* -- M. D'Alton; *University of Washington, Seattle* -- C.A. Gleason; *University of Pennsylvania, Philadelphia* -- M. Maguire; *University of Pittsburgh, Pittsburgh* -- C. Redmond; *McMaster University, Department of Clinical Epidemiology and Biostatistics* -- Robin S. Roberts; *Research Triangle Institute* -- W. Kenneth Poole; *McMaster University* -- J. Sinclair. **Data Coordination Center:** *University of British Columbia, Vancouver* -- *Joel Singer; Dale Stromberg

Table 1
Neonatal Characteristics of the Survivors of Early Inhaled Nitric Oxide Trial Evaluated at Follow-Up

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

* Babies in either group who progressed to an oxygenation index of 25 received standard iNO therapy.

Table 2**Health Status Outcomes for Survivors of Early Inhaled Nitric Oxide Trial**

Variable	Early iNO (n = 121)	Control (n = 113)	P Value	95% Confidence intervals for the difference
Hospitalized Since Discharge-n (%)	43 (35.3)	41 (36.3)	0.87 [§]	-11.1, 13.3
Home Medications:				
Bronchodilators- n (%)	27 (22)	19 (17)	0.29 [§]	-15.7, 4.8
Diuretics-n (%)	2 (1.6)	2 (1.8)	1.0 [*]	-4.5, 4.8
Anticonvulsants-n (%)	5 (4.1)	2 (1.8)	0.45 [*]	-7.9, 2.8
Tracheotomy- n (%)	2 (1.7)	0 (0)	0.50 [*]	-6.2, 1.8
Home Oxygen – n (%)	14 (11.5)	6 (5.4)	0.09 [§]	-13.7, 1.2
Home Ventilator- n (%)	3 (2.5)	0 (0)	0.25 [*]	-7.4, 0.9
Gastrostomy/Tube Feeding-n (%)	10 (8)	4 (4)	0.14 [§]	-11.4, 1.7
Use of Adaptive Equipment-n (%)	6 (5)	6 (5.5)	0.89 [*]	-6.3, 7.1
-Stroller/Wheelchair- n (%)	4 (3.4)	1 (0.9)	0.37 [*]	-7.7, 2.1
-Braces/Orthotics- n (%)	2 (1.7)	6 (5.5)	0.16 [*]	-1.2, 10.0
-Walker- n (%)	0	2 (1.8)	0.23 [*]	-1.5, 6.8

* by Fisher exact test;

[§] by Chi-square test

Table 3

Neuro-developmental impairments at 18–24 months of age in early iNO and control Infants

Variable	Early iNO (121)	Control (113)	p- value	95% Confidence Interval for the difference
Cerebral palsy-all degree – n (%)	10 (8.2)	7 (6.3)	0.58 [§]	–9.0, 5.3
Cerebral palsy-moderate to severe-n (%)	6 (4.9)	3 (2.7)	0.50 [*]	–8.2, 3.6
Any neurologic abnormality- n (%)	20 (16.4)	10 (9.2)	0.10 [§]	–16.0, 1.5
Moderate/severe neurologic abnormality-n (%)	6 (4.9)	3 (2.8)	0.51 [*]	–8.0, 3.5
Bayley MDI – mean/median (SD)	83.3/87 (21.0)	86.1/90 (19.9)	0.28#	–8.0, 2.0 ^ψ
MDI < 70- n (%)	28 (25.2)	24 (22.9)	0.68 [§]	–13.7, 9.1
Bayley PDI – mean/median (SD)	89.0/93 (17.7)	93.5/98 (18.4)	0.009#	–9.0, –1.0 ^ψ
PDI < 70- n (%)	13 (11.9)	12 (11.4)	0.91 [§]	–9.4, 8.5
Blind unilateral- n (%)	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)	0.91 [§]	–12.5, 11.0
Sensorineural loss	7 (6.8)	10 (10.0)	0.41 [§]	
Conductive loss	16 (15.5)	7 (7.0)	0.055 [§]	
Undetermined/other	1 (0.97)	7 (7.0)	0.03 [*]	
Hearing impairment requiring amplification	1 (1.0)	3 (3.0)	0.37 [*]	
Seizure disorder- n (%)	4 (3.4)	4 (3.7)	1.0 [*]	
Hydrocephalus with shunt- n (%)	0 (0)	0 (0)		
Any neuro-developmental impairment (NDI)- n (%)	34 (27.9)	28 (24.6)	0.56 [§]	–14.5, 8.0

* by Fisher exact test; # by Wilcoxon test;

[§] by Chi-square test,^ψ CI are for difference in medians for these variables