Persistent Pulmonary Hypertension of the Newborn (PPHN) Treated with Inhaled Nitric Oxide: Preliminary Hearing Outcomes

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Abstract
The hearing of 28 children, born with a diagnosis of persistent pulmonary hypertension of the newborn (PPHN) and treated with inhaled nitric oxide, was followed. The latest test for the children varied from 5 to 30 months. Of this group, three children had mild conductive hearing losses; no child had a significant sensorineural hearing loss.

Key Words: Hearing loss, nitric oxide, persistent pulmonary hypertension of the newborn (PPHN)

Abbreviations: PPHN = persistent pulmonary hypertension of the newborn, PFC = persistent fetal circulation, iNO = inhaled nitric oxide, NICU = neonatal intensive care unit, ECMO = extracorporeal membrane oxygenation, IMV = intermittent mandatory ventilation, HFOV = high-frequency oscillatory ventilation, PPM = parts per million, ABR = auditory brainstem response, VRA = visual reinforcement audiometry

This is a preliminary report on the hearing status of a group of 28 children, born with the diagnosis of persistent pulmonary hypertension of the newborn (PPHN) and treated with inhaled nitric oxide (iNO).

BACKGROUND

PPHN

PPHN, also known as persistent fetal circulation (PFC), is a clinical syndrome presenting soon after birth and characterized by progressive hypoxemia and cardiac failure. The fundamental problem is one of persistently elevated pulmonary artery resistance due to failure of normal physiologic relaxation of the pulmonary artery soon after birth, resulting in decreased blood flow through the lungs and hypoxemia. These infants differ from the premature population of the neonatal intensive care unit (NICU) in that they are generally born at term with a birth weight that is normal for gestational age.

The conventional treatments for PPHN are hyperoxia, high levels of oxygen in the blood, and hypocarbia, reduction of CO₂ in the blood. These are produced through the use of mechanical ventilation, metabolic alkalization, vasopressor support, system venous vasodilators, and, more recently, extracorporeal membrane oxygenation (ECMO). The conventional treatments are associated with substantial morbidities including sensorineural hearing loss (Naulty et al, 1986; Nield et al, 1986; Hendricks-Munoz and Walton, 1988; Kawashiro et al, 1994).

Groups lead by Roberts (Roberts et al, 1992) and Kinsella (Kinsella et al, 1993) have demonstrated the use of inhaled nitric oxide (iNO), a selective pulmonary vasodilator, as effective in
the management of PPHN. Investigators at the University of California, Irvine Medical Center (UCIMC) (Waffern et al, 1993) are in the process of comparing the efficacy and safety of iNO in a group of newborns with PPHN randomized to receive iNO with intermittent mandatory ventilation (IMV) or iNO with high-frequency oscillatory ventilation (HFOV). IMV provides a continuous flow of gas that is available during spontaneous respirations and periodically diverts gas under pressure to the infant. In HFOV, oscillators vibrate columns of air with active exhalation cycles. This provides for smaller tidal volumes, generating lower intrathoracic pressure than conventional mechanical ventilation (Hagedorn et al, 1993).

PPHN and Hearing Loss

Because survival of PPHN babies has improved, investigators have become interested in following the developmental progress of these children. Several authors have described prevalence as high as 100 percent of progressive sensorineural hearing loss in this population, even in babies who passed the auditory brainstem response (ABR) in the NICU. One group of investigators (Marron et al, 1992), however, found no sensorineural hearing loss in their group of 27 babies. A recent epidemiological study of hearing loss in the general population of children found 1 in 1278 (.08%) of non-NICU babies and 1 in 174 (.57%) of NICU babies have congenital sensorineural or mixed hearing impairment (Davis and Wood, 1992). Table 1 summarizes the reported prevalence of hearing loss in babies with PPHN.

Several investigators (Naulty et al, 1986; Nield et al, 1986; Hendricks-Munoz and Walton, 1988; Kawashiro et al, 1994) reported normal ABRs prior to discharge from the NICU in babies subsequently found to have significant sensorineural hearing losses. There is a concern about a possible progressive hearing loss in these children. The age of onset of these losses is unknown because of the timing of the hearing tests in these studies. Some hearing losses were discovered at an annual scheduled hearing test; others were tested only after parental concern. Because of the uncertainties as to the actual time of onset of hearing losses in these studies, hearing loss in children with PPHN should be studied further with an attempt to schedule hearing tests at each regularly scheduled developmental visit.

SUBJECTS AND METHODS

At the UCIMC, babies are eligible for treatment with iNO if they have a birth weight of greater than 1.5 kg and gestational ages of greater than 32 weeks. Infants must satisfy Doppler and 2-D echocardiographic diagnosis of PPHN before 12 hours of age. The babies are then randomized to either IMV or HFOV (Waffern et al, 1993).

The NO delivery apparatus has been designed to deliver measured concentrations of gas in parts per million (PPM). The infants are initially given iNO in 20 PPM for 6 to 8 hours and then, depending on the response measured by improving oxygenation, the dose of NO is decreased to 6 PPM for the duration of treatment with iNO.

If the oxygenation response of NO is sustained, the infants are maintained on their respective modes of ventilatory support while they are weaned off supplemental oxygen and positive pressure ventilation according to standard clinical practice. If, despite initial NO supplementation, there is a lack of response to therapy at the end of 6 to 8 hours, the nonresponding infant is changed to the alternate method of ventilation (e.g., a child on HFOV would be changed to IMV). Following this change, the infant continues on NO for a further 6 to 8 hours. If within these 8 hours they show...
a significant response (improved oxygenation), they continue to receive the same therapy up to 72 hours of age. If the nonresponder continues to show no response on the alternate mode of ventilation, the infant is referred for ECMO.

All babies entered into this study were scheduled for the UCI Developmental Clinic as follows: 4 to 6 months corrected age, 9 to 12 months corrected age, 18 to 24 months corrected age. This is in accordance with the guidelines of the California Children’s Services High Risk follow-up. In addition, there was a commitment to follow the hearing of each child annually until the age of 6 years. During these sessions, the child received a physical examination, a neurodevelopmental examination including the Bailey Scale of Infant Development, and the Movement Assessment for Infants. Behavioral audiology was conducted with infants 6 months of age and older.

**Hearing**

From 1993 through early 1995, 39 babies in the UCIMC NICU were eligible for iNO treatment. Of those, two were lost to follow-up, seven were referred for ECMO, and two died, leaving a cohort of 28 survivors of PPHN treated with iNO who were followed prospectively. All babies met the echocardiographic and clinical criteria for severe PPHN and were treated with 6 to 29 PPM NO (mean of 76 hours). The diagnoses are given in Table 2. There are more than 28 diagnoses as some babies had multiple disorders.

**ABR**

The ABR was used to screen hearing status in newborns. One thousand to 2000 clicks, 100 μsec in duration, were presented monaurally through earphones at intensity levels of 65 dB nHL and 35 dB nHL. The stimulation rate was 19.1 clicks per second with physiologic amplifiers set to a bandpass of 150 Hz to 1500 Hz. The recording montage consisted of high forehead to ipsilateral mastoid with contralateral mastoid, ground. Ears with repeatable responses at 35 dB nHL were judged to have a normal auditory periphery. The interpeak interval between Wave I and Wave V of the response to 65 dB nHL clicks was also used as an estimation of central conduction along the brain stem. If there was no response at 35 dB nHL, testing ascended in 10-dB steps until a response was obtained. If there was no response at 65 dB nHL, testing ascended in 10-dB steps until the limit of the equipment was reached at 85 dB nHL. In seven babies, the ABR was conducted at another facility due to transfer.

**BEHAVIORAL TEST**

Behavioral audiometry was conducted by one of the coinvestigators using visual reinforcement audiometry (VRA). Testing was conducted in a sound-treated room. The stimuli were warbled tones presented at 500 Hz, 1 kHz, and 4 kHz and calibrated live voice. Clear and consistent head turn responses to signals at a level of 25 dB HL were considered to be within normal limits. Variations of testing included having the child point to body parts and play audiometry. Testing was conducted under earphones when possible with responses at least to live voice obtained. If elevated thresholds were observed in soundfield testing, a bone-conduction oscillator was applied to one mastoid and VRA was repeated. Better thresholds obtained to bone-conducted signals were reported as an air/bone gap, at least in one ear. Immitance audiometry was conducted to evaluate middle ear function. Stapedial reflexes were tested when the tympanogram was normal.

**RESULTS**

Of the 28 babies studied, 7 were transported to other hospitals before the ABR was conducted. These seven babies were tested by ABR prior to discharge at other facilities and were judged to have normal tests. Of the 28 babies, 3 babies had abnormal ABRs.

Behavioral audiometry was conducted at the time of the developmental follow-up visits. Seventeen of the babies were tested at the UCIMC by the primary author; 11 others were tested at other facilities. Two babies, both with normal ABRs, have not had behavioral testing. Of these two children, one was tested by ABR at

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**Table 2 Diagnoses Associated with Subjects in This Study**

<table>
<thead>
<tr>
<th>Diagnoses</th>
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<tr>
<td>Sepsis</td>
<td>11</td>
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<tr>
<td>Asphyxia</td>
<td>4</td>
</tr>
<tr>
<td>Congenital syndromes</td>
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</tr>
<tr>
<td>Diaphragmatic hernia</td>
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<tr>
<td>Pulmonary hyplasia</td>
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Table 3  Babies with Abnormal Hearing Tests

<table>
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<tr>
<th>Characteristic</th>
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<th>IE</th>
<th>TD</th>
<th>LC</th>
<th>PG</th>
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<tbody>
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<td>Yes</td>
<td>Yes</td>
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<tr>
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<td>No</td>
<td>No</td>
<td>Yes</td>
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</tr>
<tr>
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<td>Yes</td>
<td>No</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
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<td>No</td>
<td>No</td>
</tr>
<tr>
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<td>Yes</td>
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<td>No</td>
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<tr>
<td>Mild hearing loss</td>
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</table>

the age of 9 days and retested by ABR at 5 months, and is now 22 months with no reported hearing problems. The other child, who is now 13 months, is reported by the pediatrician to have no problems with hearing.

Mild abnormalities (25 dB HL to 35 dB HL) in hearing have been found in three children, two had normal ABRs, and all three had flat tympanograms and were treated for middle ear pathology. For one additional child, threshold could not be determined via behavioral testing at 10 months of age, but the subsequent ABR was normal. This child had an unbalanced translocation of chromosome 4. His behavioral responses to auditory stimuli were slow and not consistent. Table 3 characterizes the children who have had at least one abnormal hearing test.

In summary, of these children who had at least one abnormal hearing test, two were judged to have normal hearing at the last test and three appeared to have mild conductive hearing losses. Among the 28 babies followed, there has been no instance of late onset sensorineural hearing loss to date.

Figure 1 shows the time of the last hearing test for the 28 infants. One baby has been followed to 30 months of age; seven children were tested between 19 to 24 months of age, six to 13 to 18 months, 1 to 6 to 12 months; and 3 have had tests from 0 to 5 months.

DISCUSSION

The hearing of 28 babies with a diagnosis of PPHN, treated with iNO, has been followed. Several authors, finding significant incidence of progressive sensorineural hearing loss in children with PPHN, have recommended close observation of hearing status (Sell et al, 1985; Nield et al, 1986; Naulty et al, 1986; Hendricks-Munoz and Walton, 1988; Kawashiro et al, 1994). The latest report of initial identification of hearing loss was at 4 years of age by Sell et al (1985) and Nield et al (1986). Most hearing loss was identified within 24 months (Sell et al, 1985; Nield et al, 1986; Naulty et al, 1986; Leavitt et al, 1987; Hendricks-Munoz and Walton, 1988; Kawashiro et al, 1994). In most reports, it is not clear whether the hearing loss occurred shortly before identification or some time before. Our duration of follow-up is 5 to 30 months.

Of our children, five failed at least one hearing test. On additional testing, two of the five were found to have normal hearing and three have mild hearing losses. These three children have been treated for otitis media and the hearing losses appear to be conductive. Our results agree with Marron et al (1992), who found no severe sensorineural hearing loss in infants with PPHN.

Of those studies that have discovered progressive sensorineural hearing losses, explanations
for the etiology of the hearing losses have been explored. Naulty et al (1986) found sensorineural hearing loss in 3/11 babies with PFC. In their protocol, all were treated with paralysis, rapid ventilation to alkalosis, and tolazoline. Gentamicin was used in the babies, and none were given furosemide. They noted progressive hearing loss in all three infants and concluded that infants with PFC may be at higher risk for sensorineural hearing loss than others in the neonatal intensive care setting.

In a study that found a 52 percent prevalence of sensorineural hearing loss, Hendricks-Munoz and Walton (1988) found that all 40 were given amikacin and furosemide, though the authors stated that amikacin peak and trough levels were not significantly different between those with hearing loss and those with normal hearing, and that there was no statistical difference in the length of time furosemide was given between the two groups. They recommended that a prospective study be performed to investigate the role of diuretic therapy in the development of hearing impairment in these infants. Sell et al (1985) found that elevated trough gentamicin levels, total gentamicin dose, and total furosemide dose did not significantly correlate with hearing loss.

Walton and Hendricks-Munoz (1991) found that the duration of hyperventilation was the only significant variable differentiating children with sensorineural hearing losses from normal-hearing children in their group of 51 infants. They speculated that cochlear integrity may have been compromised in the infants with hearing loss due to the duration of hypoxia. In contrast, Marron et al (1992) found that none of 27 infants with PPHN developed sensorineural hearing loss. In their protocol, none of the babies were hyperventilated to produce alkalosis, all infants received tolazoline (a pulmonary vasodilator), seven received furosemide, and all received gentamicin.

In summary, seven studies noted a 20 to 100 percent prevalence of sensorineural hearing loss in infants with PPHN. In six studies, all infants were hyperventilated; in one (Nield et al, 1986), the treatment was not described. Most infants received gentamicin, though studies differed in whether furosemide was given. In one study, there were no infants with sensorineural hearing loss. Interestingly, the latter group was not hyperventilated, and only 7/27 received furosemide, while most received gentamicin.

The present report is the first describing the hearing status of a group of infants with a diagnosis of PPHN who were treated with iNO. All babies were treated with gentamicin and furosemide, no infant was hyperventilated, and all were treated with iNO administered by one of two delivery methods.

Of those investigators reporting late identification of hearing loss, the latest test was reported at approximately 4 years of age (Sell et al, 1985; Nield et al, 1986). Because of the logistics of scheduled evaluations and other factors, it is difficult to ascertain whether all reported late identified hearing losses were due to difficulty with follow-up, more information as the child matured in testing, or were truly late in onset. Marron et al (1992) have tested some children with no identified sensorineural loss to the age of 6 years. Our study, with no significant hearing loss to 6 to 30 months of age, must be viewed as preliminary information that is favorable. But despite optimistic results, we are cautious in our observations and will continue to follow these children to 6 years of age.

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REFERENCES


