INHALED NITRIC OXIDE IN THE MANAGEMENT OF PERSISTENT PULMONARY HYPERTENSION OF TERM INFANTS

Jia-Yuh Chen, Pen-Hua Su, Fong-Lin Chen, and Hong-Shen Lee

Background and Purpose: Nitric oxide (NO) is an endogenous vasodilator that is responsible for regulating smooth muscle tone via changes in cyclic guanosine monophosphate (cGMP). Inhaled NO (iNO) causes pulmonary vasodilatation without affecting systemic vascular resistance. The aim of this study was to evaluate the efficacy and adverse effects of iNO therapy for the treatment of term infants with persistent pulmonary hypertension of the newborn (PPHN).

Methods: From June 1998 to June 2000, 26 term infants with PPHN were given iNO therapy. Another 21 term infants with PPHN who did not receive iNO therapy served as the control group. All patients had an oxygenation index (OI) of more than 25 at the beginning of the study. iNO was started at a dose of 20 ppm and weaned according to the response achieved within the 3 hours of treatment.

Results: The OI decreased rapidly after 30 minutes of iNO therapy and was significantly lower in the iNO group than in the control group at 30 minutes, 3, 12, and 24 hours after iNO therapy ($p<0.01$). All cases in the iNO therapy group had serum methemoglobin levels of less than 2.5% and nitric dioxide ($NO_2$) concentrations less than 2 ppm.

Conclusions: We conclude that iNO therapy produces rapid improvement in oxygenation for 24 hours without short-term side-effects in term infants with PPHN. If a high dose of NO (80 ppm) is used, serum methemoglobin and $NO_2$ values should be monitored.

Persistent pulmonary hypertension of the newborn (PPHN) is a clinical syndrome associated with elevated pulmonary vascular resistance, extracardiac right-to-left shunting through the ductus arteriosus and the foramen ovale with no structural heart disease, and arterial hypoxemia [1, 2]. Conventional management of PPHN has included the use of pharmacologic vasodilators such as tolazoline and prostaglandins D$_2$ and E$_1$ [3], respiratory alkalosis elicited by hyperventilation [4], and alkali infusion [5]. However, no specific therapy is clearly associated with a reduction in mortality [6]. In the era before inhaled nitric oxide (iNO) therapy, PPHN was often refractory and associated with a high mortality (11–48%) [6–8].

NO is an endogenous vasodilator that is responsible for regulating smooth muscle tone via changes in cyclic guanosine monophosphate (cGMP) [9]. Inhaled NO causes pulmonary vasodilatation without affecting systemic vascular resistance [9]. It has been reported that iNO therapy can improve oxygenation for patients with PPHN [10–12].

The aim of this study was to evaluate the efficacy and adverse effects of iNO therapy for the treatment of term infants with PPHN.
Patients and Methods

Between June 1998 and June 2000, 26 term infants (14 male and 12 female) with a mean gestational age of 38.5 ± 0.9 weeks (range, 38–41 wk), mean birth weight of 3.08 ± 0.42 kg (range, 2.6–4.1 kg), and PPHN (8 cases of meconium aspiration syndrome, 14 cases of neonatal asphyxia, 4 cases of pneumonia) were studied. Patients had a postductal partial pressure of arterial oxygen (PaO₂) of 50 mmHg or less on two consecutive determinations 30 minutes apart while mechanical ventilation was given at a fraction of inspired oxygen (FiO₂) of 1.0. Echocardiographic evidence of tricuspid regurgitation or shunting, either right to left or bidirectional, through the ductus arteriosus or foramen ovale was required for the diagnosis of PPHN. All 26 infants had an oxygenation index (OI) of more than 25 before iNO therapy. OI was calculated as follows: mean airway pressure x FiO₂ x 100/PaO₂ (measured from a postductal blood gas sample). Another 21 term infants (12 male and 9 female) with a mean gestational age of 38.8 ± 1.1 weeks (range, 38–41 wk), mean birth weight of 3.10 ± 0.5 kg (range, 2.65–3.7 kg), and PPHN who did not receive iNO therapy served as the control group. All patients in the control group also had an OI of more than 25 at the beginning of the study. The age at entry was 1.7 ± 0.7 days in the iNO group and 1.6 ± 0.9 days in the control group.

iNO (Linde Gas, Singapore) was delivered into the inspiratory flow of the ventilator circuit (Servo Ventilator 300 with NO, Siemens, Life Support Systems, Solna, Sweden). The device continuously sampled gas from the endotracheal side-port adapter and measured NO and nitric dioxide (NO₂) with electrochemical monitors. iNO was started at a dose of 20 ppm and weaned according to the response achieved within the first 3 hours of treatment. A positive response was inferred if there had been a decrease in OI of 25% or more, or a reduction in the FiO₂ of 0.1 or more, while the PaO₂ remained above 50 mmHg and the pH above 7.25. At 3 hours, if a positive response had been observed, the dose of iNO was decreased by 5 ppm. If tolerated, weaning was continued in steps of 3 to 5 ppm every 30 minutes to a minimum dose of 1 ppm. NO was increased by 20 ppm if infants did not show a positive response after 3 hours. The maximum dose of NO was 80 ppm. Arterial blood gas concentrations were measured before and at 30 minutes, 3, 12, 24, 48, 72, 96, and 120 hours after iNO therapy. The serum methemoglobin level was measured every 24 hours while patients were receiving iNO therapy. If the concentration of NO₂ exceeded 3 ppm or the concentration of methemoglobin exceeded 7%, the iNO dose was decreased.

Values are expressed as mean ± standard deviation. The significance of differences between values was evaluated by two-factor repeated measures ANOVA and Student’s t-test. Frequencies in various groups were compared by the chi-square test. A p value of less than 0.05 was considered statistically significant. The study was approved by the hospital ethics committee. Informed consent was obtained from the parents of all studied infants.

Results

One patient with PPHN received a maximum iNO dose of 80 ppm, one patient a maximum of 60 ppm, five patients a maximum of 40 ppm, and 19 patients a maximum of 20 ppm.

Ofs after iNO therapy in term infants with PPHN and in controls are shown in the Table. The OI was similar in the treatment and control groups at the beginning of the study, but decreased rapidly after 30 minutes of iNO therapy and was significantly lower (p < 0.01) in the iNO group than in the control group at 30 minutes, 3, 12, and 24 hours after iNO therapy. No significant difference was found in the OI between the two groups at 48, 72, 96, and 120 hours after the start of treatment in the iNO group. No short-term side effects were found.

There was no significant difference in the duration of intubation between the control and iNO groups (9.5 ± 56 vs 9.1 ± 4.7 d). The mean duration of iNO therapy was 4.8 ± 1.2 days. Five patients in the control group and three patients in the iNO group died. One patient in the iNO group died due to intracranial hemorrhage. All patients in the iNO group had methemoglobin levels of less than 2.5% and NO₂ concentrations of less than 2 ppm.

Table. Oxygenation index in term infants with PPHN treated with inhaled nitric oxide and in controls

<table>
<thead>
<tr>
<th></th>
<th>Nitric oxide group (n = 26)</th>
<th>Control group (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pretreatment</td>
<td>33.8 ± 6.6</td>
<td>33.6 ± 3.7</td>
</tr>
<tr>
<td>30 minutes</td>
<td>17.4 ± 7.3</td>
<td>28.3 ± 4.2*</td>
</tr>
<tr>
<td>3 hours</td>
<td>15.6 ± 5.9</td>
<td>24.6 ± 6.0*</td>
</tr>
<tr>
<td>12 hours</td>
<td>12.3 ± 5.4</td>
<td>21.2 ± 8.2*</td>
</tr>
<tr>
<td>24 hours</td>
<td>11.5 ± 5.5</td>
<td>18.1 ± 8.7*</td>
</tr>
<tr>
<td>48 hours</td>
<td>11.2 ± 5.8</td>
<td>13.4 ± 11.1</td>
</tr>
<tr>
<td>72 hours</td>
<td>10.9 ± 6.2</td>
<td>12.0 ± 11.4</td>
</tr>
<tr>
<td>96 hours</td>
<td>9.4 ± 8.0</td>
<td>11.7 ± 10.7</td>
</tr>
<tr>
<td>120 hours</td>
<td>8.5 ± 4.9</td>
<td>8.9 ± 7.7</td>
</tr>
</tbody>
</table>

Values expressed as mean ± standard deviation. *p < 0.01
Nitric Oxide Therapy in Persistent Pulmonary Hypertension of the Newborn

**Discussion**

NO is a colorless gas that has been identified as endothelial-derived relaxing factor [13]. It is capable of activating cytosolic guanylate cyclase and raising intracellular levels of cyclic guanylate monophosphate (cGMP), thereby causing profound vascular smooth muscle relaxation [9]. Inhaled NO relaxes preconstricted pulmonary blood vessels without causing concomitant systemic hypotension. The selectivity of NO for pulmonary vasorelaxation is related to its direct action on pulmonary vascular smooth muscle and its rapid inactivation by hemoglobin [14].

PPHN is a syndrome of acute respiratory failure, and most commonly occurs in term infants who have underlying disease such as meconium aspiration syndrome, pneumonia, sepsis, congenital diaphragmatic hernia, respiratory distress syndrome, or asphyxia [9]. Conventional management of PPHN has included the use of respiratory alkalosis elicited by hyperventilation [4] and the use of pharmacologic vasodilators [6]. Drummond et al found a consistent and sustained rise in PaO2 once the PaCO2 was reduced to 19 to 22 mmHg and the pH raised to 7.55 to 7.60, particularly in infants with primary PPHN [4]. In addition, at low PaCO2, myocardial blood flow falls by 20% to 25% [15], and there is a 50% reduction in cerebral blood flow that may result in neuronal ischemia [16]. The main hazard of hyperventilation is that it increases the risk of air leak and subsequent chronic lung disease [16]. Vasodilator drugs, primarily tolazoline, are also commonly used to treat PPHN [6]. These dilate the pulmonary vasculature and can also cause systemic hypotension [16]. Currently, hyperventilation and tolazoline are seldom used to treat term infants with PPHN. In this study, we found that iNO therapy could produce an acute improvement in oxygenation for 24 hours without short-term side-effects in term infants with PPHN. The same findings have also been reported previously [10–12, 17, 18]. The use of iNO therapy may reduce the need for more invasive treatments such as extracorporeal membrane oxygenation. Kusuda et al found that the mean pulmonary artery pressure (PAP) increased during hypoxic breathing [19]. Treatment with iNO can decrease PAP significantly and does not change mean systemic artery pressure and cerebral blood flow.

The major safety concerns are methemoglobinemia and elevated NOx concentrations. All cases treated with iNO in this study had serum methemoglobin levels of less than 2.5% and NOx concentrations of less than 2 ppm during the study period. It has been reported that methemoglobinemia of more than 7% and NOx concentrations of more than 3 ppm may occur if a high dose of NO (80 ppm) is used, and that iNO concentration should be reduced or discontinued if either of these conditions develops [11, 12].

It has been reported that iNO may cause platelet dysfunction [20–22]. In the present study, there was no significant difference in the incidence of intracranial hemorrhage between the iNO and control groups. Abrupt withdrawal of iNO during prolonged therapy may cause a rebound effect [23]. In this study, we reduced the iNO concentration to 1 ppm before discontinuing iNO therapy, as this has been suggested to minimize rebound effects [24]. Assessment of the exposure of medical personnel to NO during iNO treatment of neonatal and pediatric patients has been studied by Phillips et al [25]. Detectable exposure to NO and NO2 were found to be brief, infrequent, and well below the Occupational Safety and Health Administration permissible exposure limits [25]. In our neonatal intensive care unit, scavenging systems remove constant flow and exhalation gases, including NO and other oxides of nitrogen. Constant evaluation for exposure to the potential toxic gases from the circuit is of paramount importance for the safe administration of iNO therapy. The Neonatal Inhaled Nitric Oxide Study Group found that iNO was not associated with an increase in neurodevelopmental, behavioral, or medical abnormalities at 2 years of age [26].

We conclude that iNO can produce an acute improvement in oxygenation for 24 hours without short-term side-effects in term infants with PPHN. Because of the small numbers in this trial, further evaluation and long-term follow-up are necessary to establish long-term safety and efficacy for iNO therapy in neonates.

**References**


