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ORIGINAL ARTICLE

Randomized controlled trial of early compared with delayed use of inhaled nitric oxide in newborns with a moderate respiratory failure and pulmonary hypertension

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Objective: To evaluate whether early treatment with inhaled nitric oxide (iNO) will prevent newborns with moderate respiratory failure from developing severe hypoxemic respiratory failure (oxygenation index (OI) $\geqslant 40$).

Study Design: A total of 56 newborns with moderate respiratory failure (OI between 10 and 30) were randomized before 48 h after birth to early treatment with 20 p.p.m. of iNO (Early iNO group, $n = 28$) or conventional mechanical ventilation with FiO_2 1.0 (Control group, $n = 28$). Infants received iNO and/or high-frequency oscillatory ventilation (HFOV) if they developed an OI > 40.

Result: 7 of 28 early iNO patients (25%) compared to 17 of 28 control patients (61%) developed an OI > 40 ($P < 0.05$). In the Early iNO group mean OI significantly decreased from 22 (baseline) to 19 at 4 h ($P < 0.05$) and remained lower over time: 19 (12 h), 18 (24 h) and 16 at 48 h. In contrast, OI increased in the Control group and remained significantly higher than the Early iNO group during the first 48 h of study: 22 (baseline), 29, 35, 32 and 23 at 4, 12, 24 and 48 h, respectively ($P < 0.01$). Of 17, 6 control patients who developed an OI > 40 were successfully treated with iNO. Nine of the remaining eleven control patients and six of seven Early iNO patients who had an OI > 40 despite use of iNO responded with the addition of HFOV. One patient of the Early iNO group and two of the Control group died. Median (range) duration of oxygen therapy was significantly shorter in the Early iNO group: 11.5 (5 to 90) days compared to 18 (6 to 142) days of the Control group ($P < 0.03$).

Conclusion: Early use of iNO in newborns with moderate respiratory failure improves oxygenation and decreases the probability of developing severe hypoxemic respiratory failure.

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Introduction

Persistent pulmonary hypertension of the newborn (PPHN) is a serious condition that may accompany respiratory diseases such as meconium aspiration syndrome, pneumonia, respiratory distress syndrome and congenital diaphragmatic hernia.[1,2] Despite the variety of causes, similar physiopathologic changes characterize this syndrome: a persistently raised pulmonary vascular resistance after birth, which leads to severe hypoxemia due to extrapulmonary shunting. This disease can progressively get worse, due to the fact that sustained hypoxia may injure pulmonary vasculature inducing remodeling and making it unresponsive to vasodilators.[3,4] The sustained hypoxemia and the high oxygen concentrations, and elevated ventilator pressures/volumes needed to treat these infants, may lead to further lung injury and myocardial dysfunction. This sequence of events may result in death, an occurrence made more common in countries that do not have access to extracorporeal membrane oxygenation (ECMO), where mortality of this syndrome is between 10 and 40%.[1,2,5,6]

Inhaled nitric oxide (iNO) has been shown to be an effective treatment for PPHN.[7–10] Several randomized clinical trials have shown that iNO significantly improves oxygenation and decreases the need of ECMO or incidence of death in near-term infants with hypoxic respiratory failure.[11–13] However, their response to iNO is not ideal and ranges between 50 and 60%. This may be due to the fact that in most studies, infants were critically ill, either fulfilling ECMO criteria (oxygenation index (OI) $\geqslant 40$) or had severe lung disease and vascular damage, and were unresponsive to therapy. It has been also shown that iNO may attenuate lung inflammation and pulmonary vascular remodeling in experimental lung-injured models.[14,15] On the basis this information, we hypothesized that early treatment with iNO in newborns with

moderate respiratory failure (OI between 10 and 30) and pulmonary hypertension would improve oxygenation and attenuate the development of severe hypoxemic respiratory failure (OI > 40).

Methods

This was a prospective, randomized controlled and unblinded trial performed in two neonatal intensive care units in Santiago, Chile between March 1997 and December 2003. This study was approved by the investigational review board of the Pontificia Universidad Católica de Chile School of Medicine and by the ethics committees of both hospitals. A written informed consent was obtained from the parents of all infants at the time of enrollment.

Study population

Near-term infants ($\geqslant$35 weeks gestation) with birth weights >2000 g and $\leqslant$48 h old were eligible for enrollment. We included 56 infants requiring mechanical ventilation with moderate hypoxemic respiratory failure with an OI between 10 and 30. This was calculated on two consecutive measurements of post-ductal arterial blood gases and after ventilatory support had been adjusted to achieve a PCO_2 < 60 mm Hg and pH > 7.25. All infants had a previous echocardiogram, which was negative for cardiac anomalies and had evidence of pulmonary hypertension. This was defined as a tricuspid insufficiency jet with an estimated systolic pulmonary artery pressure $\geqslant$2/3 of systemic systolic arterial blood pressure and/or evidence of right-to-left shunting through the foramen ovale or ductus arteriosus. Exclusion criteria included the presence of a life-threatening congenital anomaly, suspected or confirmed chromosomal abnormality, congenital heart disease, congenital diaphragmatic hernia and other forms of lung hypoplasia syndromes.

Protocol

Infants were randomized using sequenced sealed envelopes into two study groups:

(1) Early iNO group, which received iNO with conventional mechanical ventilation, and
(2) Control group, which received conventional mechanical ventilation with 1.0 FiO_2.

Patients in both groups were kept on conventional mechanical ventilation and settings were adjusted to keep PaO_2 between 60 and 100 mm Hg and $PaCO_2$ between 35 and 50 mm Hg. Inotropic drugs were administered to keep mean systemic arterial blood pressures $\geqslant$50 mm Hg. Sodium bicarbonate was given if necessary to keep the arterial pH between 7.35 and 7.5.

Inhaled nitric oxide was started at 20 p.p.m. in the Early iNO group and ventilatory settings were not changed during the first 30 min unless acute deterioration occurred. This initial dose was kept constant for the first 4 h. Attempts were made to reduce iNO dose in a stepwise manner by 5 p.p.m. every 2 to 4 h until 5 p.p.m. was reached. If condition of the patient deteriorated with the reduction of dose, the dose was increased to obtain the minimal dose necessary to keep oxygen saturations $\geqslant$88%. The new dose was maintained for at least 24 h. Attempts were made to discontinue iNO, if the patient had been stable on an iNO dose $\leqslant$5 p.p.m. and with an OI < 10 for 24 h. If this was not possible, iNO was continued for an additional 24 h.

Treatment failure was defined as a worsening in respiratory status during first 48 h of treatment based on an increase in the OI to >40. Patients in the Control group who reached an OI > 40 were treated with iNO. Infants in both groups who persisted with an OI >40 despite iNO were treated with high-frequency oscillatory ventilation (HFOV) and iNO. ECMO treatment was not available in Chile during the study period.

Inhaled nitric oxide was delivered using a 990 p.p.m. sealed tank (AGA Chile SA, Santiago, Chile/INO Therapeutics; Port Allen, LA, USA) and iNO and NO_2 levels were continuously measured by electrochemical cell analyzers (PAC II Analyzer; Draeger, Lübeck, Germany and NOxBox I; Bedfont, Rochester, England, UK). An indwelling arterial line was placed in all patients to monitor systemic arterial blood pressure and draw serial arterial blood gases at baseline, 4, 12 and 24 h and at least every 12 h thereafter while the patient was receiving iNO. Methemoglobin levels were also measured at baseline and every 24 h while the patient was on iNO. All these variables along with the clinical data of patients including pregnancy history and delivery, birth weight, age, and the presence of other complications of the neonatal period such as intraventricular hemorrhage, pneumothorax, chronic lung disease (defined as oxygen dependence for 28 or more days and an abnormal chest X-ray), were recorded on standardized forms and saved in a computer database.

Statistical analyses

Sample size was estimated based on previous data.[6] Assuming that 60% of Control group patients would develop an OI $\geqslant$ 40, we calculated that approximately 54 patients would need to be enrolled to provide the study with 80% power to detect a reduction in treatment failure to 33% in the Early iNO group, with a type I error of 0.05. We conducted the analysis according to the intention-to-treat principle. Clinical and demographic characteristics were compared using the Student's *t*-test and analysis of variance for continuous variables with normal distribution, and Mann–Whitney test for independent samples for those with a not normal distribution. Categorical variables were compared using χ^2-test and if the expected number of observations was less than 5, Fisher's exact test was used instead. A *P*-value $\leqslant$0.05 was considered significant.

Results

A total of 56 newborns were enrolled in this study, 28 in each group. As seen in Table 1, characteristics of infants did not differ

Table 1 Patient characteristics

	Early iNO (n = *28*)	*Controls* (n = *28*)	P-*value*
Birth weight (g)	3225 ± 410	3157 ± 475	NS
Gestational age (weeks)	38 ± 1.5	37.5 ± 1.7	NS
5′ Apgar, median (range)	8 (3–9)	8 (2–9)	NS
Gender (Male/Female)	15/13	16/12	NS
Age at enrollment (h)	25 ± 14	26 ± 12	NS
Inborns, *n* (%)	6 (22)	6 (22)	NS
Inotrope use, *n* (%)	21 (75)	20 (71)	NS
Primary diagnosis (n)			
Meconium aspiration	8	7	
Pneumonia/sepsis	7	9	NS
RDS/HMD	11	9	
Idiopathic/other	2	3	

Abbreviations: HMD, hyaline membrane disease; iNO, inhaled nitric oxide; RDS, respiratory distress syndrome.

Table 2 Respiratory variables at enrollment

	Early iNO (n = *28*)	*Controls* (n = *28*)	P-*value*
FiO_2	0.97 ± 0.06	0.96 ± 0.08	NS
Mean airway pressure (cm H_2O)	14.2 ± 3.1	14.3 ± 3.5	NS
Oxygenation index	22.2 ± 4.3	21.9 ± 5.3	NS
PaO_2 (mm Hg)	61 ± 14	64 ± 25	NS
$PaCO_2$ (mm Hg)	39 ± 8	40 ± 10	NS
pH	7.4 ± 0.1	7.35 ± 0.1	NS
Surfactant use, *n* (%)	19 (68)	20 (71)	NS
PIP (cm H_2O)	30.3 ± 6	31.7 ± 7	NS
PEEP (cm H_2O)	4.3 ± 1.0	4.4 ± 1.2	NS
Ventilator rate (breaths/min)	59 ± 10	57 ± 9	NS

Abbreviations: iNO, inhaled nitric oxide; NS, not significant; PEEP, positive end expiratory pressure; PIP, peak inspiratory pressure.
Results are mean ± s.d., unless specified.

between the groups in terms of birth weight, age at randomization, condition at birth and the underlying respiratory diseases associated with their respiratory failure.

The baseline ventilatory and hemodynamic conditions were also similar between the Early iNO and Control groups at the time of enrollment (Table 2). The infants required moderately high levels of conventional ventilatory support, with FiO_2 ranging between 0.75 and 1.

Acute changes in oxygenation

Infants assigned to the Early iNO group had a significant increase in PaO_2 from baseline, which led to a significant decrease in their OI: (mean ± s.d.) OI decreased from 22.2 ± 4.3 at baseline to 19.0 ± 7.2 at 4 h ($P<0.05$), which continued decreasing over time (Figure 1). In contrast, OI increased in the Control group and remained significantly higher than the Early iNO group during the first 48 h of study ($P<0.01$).

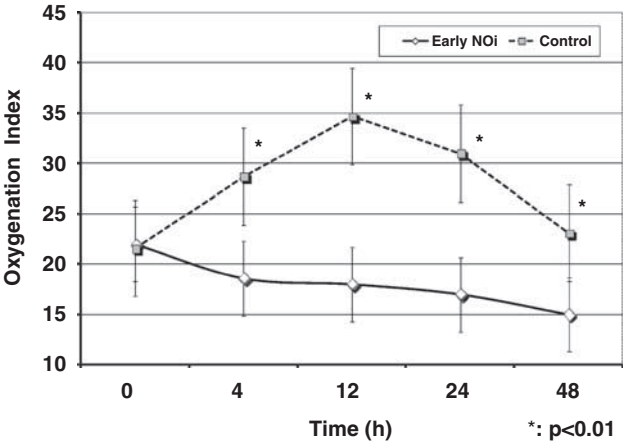

Figure 1 Change in oxygenation index over time in the two study groups. Points represent mean ± s.e.m. The oxygenation indexes (OIs) were significantly higher after baseline in the Control group ($P<0.01$).

Table 3 Respiratory outcomes

	Early iNO (n = *28*)	*Controls* (n = *28*)	P-*value*
Treatment failure (OI ⩾40), *n* (%)	7 (25)	17 (61)	<0.05
Deaths (*n*)	1	2	NS
Mech. ventilation days, median (range)	6 (3–28)	8 (4–37)	NS
Oxygen therapy days, median (range)	11.5 (5–90)	18 (6–142)	<0.03
Chronic lung disease, *n* (%)	4/27 (15)	7/26 (27)	NS

Abbreviations: iNO, inhaled nitric oxide; NS, not significant; OI, oxygenation index.

Treatment failure

Seven of 28 infants (25%) receiving early iNO and 17 of 28 infants (61%) on conventional therapy developed an OI >40 treatment failure ($P<0.05$). Of 17, 6 control patients who developed an OI>40 were successfully treated with iNO subsequently. Nine of the remaining eleven control patients and six of seven Early iNO patients who had an OI > 40 despite iNO responded with the addition of HFOV. One patient of the Early iNO group and two of the Control group died.

Table 3 shows the respiratory outcomes of both groups: duration of mechanical ventilation was not significantly different, whereas duration of oxygen therapy was significantly lower among infants of the Early iNO group ($P<0.03$). This was confirmed with the survival analysis for the need of oxygen therapy, which was significantly higher over time in Control group (Figure 2).

Patients treated with iNO did not have elevated blood levels of methemoglobin or high levels of NO_2 in the ventilatory circuit. Also, there were no differences between the groups in the incidence of other neonatal complications such as bleeding and/or coagulation disorders, hypotension or infections.

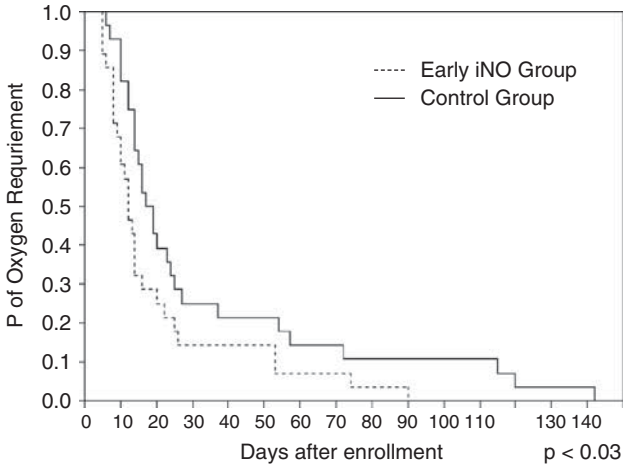

Figure 2 Survival plot of probability of oxygen requirement over time in study groups. As observed, infants of the Early iNO (inhaled nitric oxide) group spent significantly less time with oxygen therapy compared with those of the Control group ($P<0.03$).

Discussion

The present study shows that early treatment with iNO in neonates with moderate hypoxemic respiratory failure increases oxygenation and decreases the probability of developing severe PPHN/respiratory failure (OI>40). The observed improvement in oxygenation with iNO therapy is consistent with the results of several randomized controlled studies.[11–13] The novel aspect of this trial is the early use of iNO in the disease's course in centers without ECMO availability, preventing the development of severe respiratory failure in most treated infants. This reduction in PPHN severity may decrease mortality and respiratory sequelae in patients with respiratory failure in places where ECMO is not available. As the observed mortality was low in both groups, unfortunately this study was not powered to confirm this point. Until now, most published reports have not shown a decrease in mortality with iNO, possibly this can be explained because ECMO was used in infants when iNO failed.

Along with their oxygenation improvement, infants who received early iNO required less time with oxygen supplementation and therefore their oxygen exposure was reduced. It is possible that this strategy of early iNO use may decrease lung damage and the severity of chronic lung disease in infants with moderate respiratory failure. Most studies have not shown a clear benefit of iNO in long-term respiratory outcomes. In the majority of these studies, treated infants were sicker, enrolled later in the disease course and all of them had ECMO as a rescue therapy when iNO failed. In this study however, ECMO was not available and therefore those infants whose oxygenation did not improve remained either on conventional or HFOV with high settings and elevated oxygen concentrations for longer periods of time.

There are few studies that have evaluated a relatively 'early' iNO use strategy. Davidson *et al*.[16] did not find clear differences in the length of oxygen supplementation or mechanical ventilation; however the studied infants seem sicker and ECMO was available. The Franco-Belgium Collaborative NO Trial Group[17] showed a decrease in length of mechanical ventilation and a lower proportion of infants requiring oxygen at 28 days when iNO was used in near-term infants younger than 7 days with moderate respiratory failure (OI of 15 to 40). Sadiq *et al*.[18] compared iNO treatment with standard treatment in near-term infants with moderate PPHN (alveolar-arterial oxygen gradient, ($AaDO_2$) of 500 to 599 torr), they found that iNO treatment improved PaO_2, reduced the amount of ventilatory support and prevented progression to severe PPHN defined as $AaDO_2 > 600$ torr. Infants of the Control group also received iNO if their $AaDO_2$ was >600, there were no differences in need for ECMO or incidence of death. More recently, Konduri *et al*.[19] conducted a large randomized controlled multicenter trial in near-term infants who were <14 days old with moderate respiratory failure (OI of 15 to 25). They compared early use of iNO with a Control group that received simulated initiation of iNO. Infants received standard iNO if they developed an OI $\geqslant$25. Although the Early iNO group had significantly better initial oxygenation and Control group progressed to standard iNO and developed an OI >40 more often, the incidence of death, ECMO use and other respiratory outcomes was not different. Although this study evaluated a population similar to our study, controls had a lower threshold to receive standard iNO (OI >25) and ECMO was used as a back-up therapy. In addition, the mean OI at entry was approximately 20, which was close to the threshold to receive standard iNO. In fact, a significantly larger proportion of the control infants (54%) received standard iNO, and therefore there was not a clear separation between the Early and the Control groups that can explain the lack of a clear treatment effect. A subgroup analysis of the 176 infants enrolled at an OI of 15 to 20 in that study showed a trend for lower incidence of ECMO use/mortality (10% with Early iNO vs 18% in the Control group, $P = 0.12$).[19,20] Also, the incidence of ECMO use in the whole study (11%) was lower than that observed in previous large clinical trials with iNO (approximately 40%). Therefore, similar to our results, these data indicate that the earlier use of iNO may be associated with further reductions in short-term respiratory morbidity. There are several recently published studies that evaluated iNO treatment in premature infants. Although different strategies were evaluated and results are conflicting, it seems that early routine use in mildly sick ventilated preterm infants may improve their survival without bronchopulmonary dysplasia.[21–24] This study also supports a possible beneficial effect of early iNO therapy in decreasing lung damage.

There are a number of factors that limit the impact of our trial. First, this trial was not blind because we had limited numbers of personnel and equipment to have independent teams masked to the assigned therapy or in charge of the iNO administration and monitoring. Second, this study took more than 5 years to be

completed, because of the difficulty in early recruitment of these patients and also because we had a limited and interrupted supply of nitric oxide during the study period. After the design and onset of this study, it became known that the use of HFOV improves the oxygenation response to iNO in newborns with hypoxic respiratory failure due to parenchymal lung disease.[25] However, because we had a limited availability of HFOV during the study period, this mode of ventilation was added to iNO only in infants who persist with severe respiratory failure (OI>40) despite the use of iNO.

Despite these limitations, we believe that the observed results in improved oxygenation and mitigation of the development of severe PPHN/respiratory failure (OI >40) with early iNO use are important, and support a strategy that may ameliorate the development of lung injury. Further studies are needed to confirm the impact of this strategy of iNO use in long-term respiratory outcomes.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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