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A pilot study of inhaled nitric oxide in preterm infants treated with nasal continuous positive airway pressure for respiratory distress syndrome

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Abstract *Objective:* To explore the acute effects of inhaled nitric oxide (iNO) on oxygenation, respiratory rate, and CO_2 levels in spontaneously breathing preterm infants treated with nasal continuous positive airway pressure (nCPAP) for moderate respiratory distress syndrome (RDS). *Design and setting:* Randomized, prospective, double-blind, cross-over study in the neonatal intensive care units of a university hospital. *Patients:* 15 infants treated for RDS, with a median gestational age of 32 weeks (27–36), birth weight 1940 g (1100–4125), and postnatal age at the beginning of study 23 h (3–91). nCPAP pressure was kept constant at 4.3 cmH_2O (3.4–5.1). *Interventions:* We examined effects on gas exchange and vital signs during a 30-min exposure to 10 ppm iNO or placebo gas (nitrogen). *Results:* Before administering test gases the baseline arterial to alveolar oxygen tension ratio ($aAPO_2$) was 0.19±0.06. $aAPO_2$ remained unchanged during placebo but increased to 0.22±0.05 (+20%) during iNO exposure. Respiratory rate and arterial carbon dioxide tension remained unchanged, as did heart rate, blood pressure, and methemoglobin. Follow-up at 30 days of age showed no deaths, delayed morbidity, or need for supplemental oxygen. *Conclusions:* Adding 10 ppm nitric oxide to nasal CPAP treatment in preterm infants suffering from RDS results in a moderate but statistically significant improvement in oxygenation, with no effect on respiratory drive or systemic circulatory parameters.

Keywords Nitric oxide · Administration, inhalation · Continuous positive airway pressure · Respiratory distress syndrome, newborn

Introduction

In the early 1990s inhaled nitric oxide (iNO) was seen as an interesting therapeutic option on the basis of its pharmacodynamic action as a selective pulmonary vasodilator. Since then it has become a formally approved drug in the European Union and the United States, being a powerful therapeutic tool to improve oxygenation in severe hypoxemic respiratory failure. Particularly in term and near-term newborn infants the benefits of iNO have been established in randomized placebo-controlled studies [1, 2, 3].

In recent years new and interesting effects of iNO, in addition to improving oxygenation, have been observed in animals and man. These effects may modify pathophysiological events in the lung during respiratory distress. Early administration of iNO has been shown to be anti-inflammatory [4, 5], to be anti-proliferative on vascular smooth muscle cells [6, 7], and to promote normal lung development [8]. It is now known that NO after pulmonary absorption can be transported outside the lung and used in redox-based signaling [9, 10, 11]. Some extrapulmonary effects may be undesirable, such as reversible changes in kidney function [12, 13].

Mechanical ventilation (MV) and intubation have so far been a requirement for iNO therapy. However, these interventions may independently add to morbidity [14]. We have developed and tested a delivery system enabling the combined treatment of iNO and nasal CPAP [15] as there are data to indicate that iNO given in an unpressurized system has little effect on pulmonary hypertension and none on oxygenation [16]. In the present pilot study we examined the hypothesis that an acute improvement in oxygenation can be achieved by combining iNO (vasodilatation and matching of perfusion to ventilation) and nasal CPAP (lung recruitment) in moderate respiratory distress syndrome (RDS), at a stage at which a definite decision to administer surfactant had not yet been taken. In the future a combination of these different therapeutic options may prove useful [17, 18, 19] as increased pulmonary artery pressures are also an integral part of RDS, especially in patients with a limited or short-lived response to surfactant replacement [20]. Before such a combined therapy can be studied in larger randomized studies, it is pivotal to demonstrate whether CPAP delivery of iNO is powerful enough to create a physiological response in moderately ill patients. One way of doing so is to study whether iNO/CPAP can enhance oxygenation in neonates with RDS *prior to* administration of surfactant. Data from this study were presented at the 2004 PAS Annual Meeting [21].

Methods and materials

Subjects

We included 15 preterm infants treated with nasal CPAP for moderate RDS. The median gestational age was 32 weeks (range 27–36) and birth weight 1940 g (1100–4125). The postnatal age at inclusion was 23 h (3–91) and all patients had Apgar scores of 7 or higher.

Inclusion criteria were a CPAP of 4 cmH_2O or higher, arterial to alveolar oxygen tension ratio between 0.13 and 0.22 [$aAPO_2=PO_2/(FIO_2 \times 0.95-PaCO_2)$] [22] and a diagnosis of RDS based on the clinical picture (retractions, grunting, increasing demand for supplemental oxygen) and a typical radiographic appearance [23]. All infants had an umbilical arterial catheter to measure invasive blood pressure and arterial blood gases. Exclusion criteria were: birth weight less than 1 kg, gestational age less than 27 weeks, congenital diaphragmatic hernia, intracranial hemorrhage or other signs of severe brain damage, VOC, air leak, meconium aspiration, Apgar score at 5 min of 4 or less, umbilical cord pH less than 6.9, and infection. Infection was defined as a positive blood/spinal fluid culture, C-reactive protein level of more than 50 mg/l, or a white blood cell count of 9×10^9/l or lower.

We obtained signed informed parental consent, and approval for the study was granted by the Karolinska Institutet Regional Ethics Committee and the Swedish Medical Product Agency. The study was performed at the neonatal ICUs of Karolinska University Hospital, adhering to the standards of good clinical practice. None of the subjects had received sedation, and none was on any supporting therapy such as catecholamines.

Experimental protocol

We designed a system for the simultaneous delivery of iNO and nCPAP [15] based on the Infant Flow (Electro Medical Equipment, Brighton, UK) [24] as it has little variance in CPAP pressure and low work of breathing [25, 26]. A small chamber designed to achieve rapid mixing of inspired gases was inserted into the flow channel 27 cm from the nose. A midstream sampling port was located at the end of the chamber. Sample gas was analyzed continuously by a fast paramagnetic O_2 analyzer [27] that is unaffected by NO/NO_2 (personal communication, P. Merilainen; OscarOxy, DatexOhmeta, Helsinki, Finland). This allowed adjustments to provide a fraction of inspired oxygen identical to that measured before dilution of inspired gas by iNO or placebo.

We first introduced nitrogen, using a flow of 10% of the total flow which was between 7–8 l to set nCPAP pressure (>4 cmH_2O) and simultaneously adjusted oxygen concentration. To counter the dilution of O_2 with nitrogen present in the study gases the oxygen setting of the Infant Flow Driver was adjusted by a factor of 1.11, thereby achieving an unaltered O_2 to the patient. The target saturation (SPO_2) for the study was 94±3%. CPAP was kept constant by minor flow adjustments. Exhaled gases were diverted out of the incubators. Both study gases were stored in identical cylinders from INO Therapeutics (Clinton, N.J., USA). Cylinder concentration for NO was 100 ppm in nitrogen. Inhaled concentrations of iNO and NO_2 were measured by electrochemical cells NoxBox (Bedfont Scientific, Rochester, UK) [15].

Following baseline recordings for 15 min, iNO at 10 ppm or N_2 (placebo) was administered for 30 min in a cross-over and blinded design: one investigator, responsible for the care of the patient, blood gas sampling, and recording of patient data, remained unaware of the placebo-iNO sequence. A coinvestigator monitored oxygen, NO, and NO_2 levels and administered the different study gases.

After a 15-min washout period, using the same flow of nitrogen from the *open* source to maintain oxygen concentration, a second 30-min gas exposure was started. The order of placebo/iNO administration was determined by a computer-generated random sequence placed in 25 sealed envelopes. At the end of each exposure a period of weaning was performed according to a predetermined protocol (5% increase in FIO_2 and stepwise decrease in study gas over 5 min).

Data collection

Vital signs were collected every 5 min. Umbilical artery (postductal) blood gases were taken before, during (after 25 min exposure), and 15 min after completed weaning off placebo or iNO. Side effects such as methemoglobin formation during or rebound hypoxia upon discontinuation of iNO were also monitored. All analyses of blood including determinations of arterial blood gases were provided by a quality accredited hospital laboratory. Peripheral oxygen saturation (SPO_2) from the right hand, transcutaneous measurements of arterial oxygen tension ($P_{tc}O_2$), and carbon dioxide tension ($P_{tc}CO_2$), heart rate derived from three-point electrocardiography, and measurement of invasive arterial pressures were recorded by a patient monitoring system (M1095A, Hewlett Packard, Boeblingen, Germany). CPAP was checked repeatedly with a precision pressure monitor Digitron 2081P (Digitron, Torquay, UK).

Statistical analyses

The primary outcome variable was changes in oxygenation measured as $aAPO_2$. Secondary outcomes were SPO_2, $PaCO_2$, respiratory rate, heart rate, and invasive arterial blood pressure. Sample

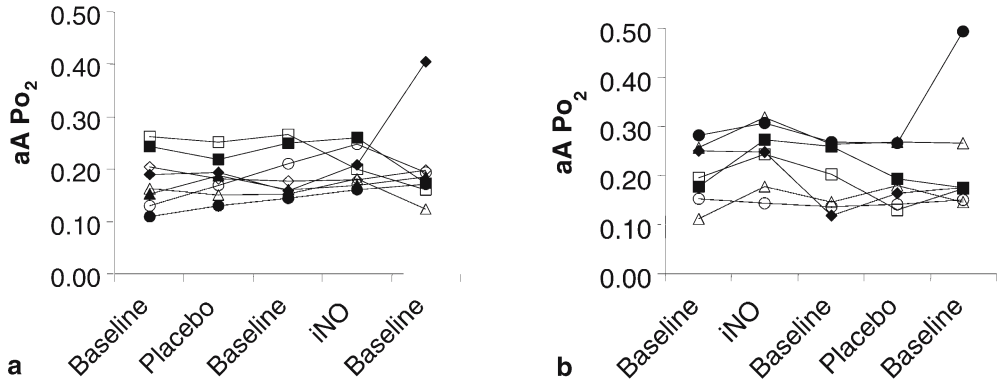

Fig. 1 Course of arterial-alveolar oxygen tension ratio ($aAPO_2$) over time for each infant. Each baseline lasted 15 min with arterial blood sampling at the end. Each exposure to placebo or to iNO lasted 30 min with arterial blood sampling performed at 25 min, followed by weaning. **a** Infants randomized to cross-over sequence placebo-inhaled nitric oxide (n=8). **b** Infants randomized to cross-over sequence inhaled nitric oxide-placebo (n=7)

Table 1 Outcome data

	Baseline	Placebo	iNO 10 ppm	p[a]
$aAPO_2$	0.19±0.06	0.19±0.05	0.22±0.05	0.006
SPO_2 (%)	94±2	93±4	96±3	0.012
Respiratory rate (bpm)	63.0±16	59±16	68±20	n.s.
$PaCO_2$ (kPa)	7.03±1.19	6.97±1.24	6.92±1.13	n.s.
Mean arterial pressure (mmHg)	38.5±7.1	39.4±8.0	38.8±8.3	n.s.
Heart rate (beats/min)	145.4±9.9	147.0±7.8	146.1±12.9	n.s

[a] iNO vs. placebo

size calculations suggested 11 patients in each sequence to detect a mean treatment difference in $aAPO_2$ of at least 15% (power=80%, p<0.05, and assuming a standard deviation of within-subject differences of 25%). All treatment comparisons used a standard 2×2 cross-over model, studying the within-subject treatment differences of the two sequences, thereby controlling for subject and period effects. Carry-over effects from first treatment period were considered negligible. Statistical comparisons were performed using paired t test and 95% confidence intervals (CI) for treatment effects were calculated. Differences at a p value less than 0.05 were considered significant. Results are presented as mean ±SD. The design used in this study and the method for statistical analysis are described elsewhere [28]. During the study period an increase in the use of surfactant installation by means of a brief intubation during nCPAP treatment was seen [29]. This resulted in a sharp decline in the number of patients fulfilling the stipulated inclusion criteria regarding oxygen demand. Therefore the recruitment was stopped after 15 inclusions.

Results

Before administering test gases the baseline $aAPO_2$ was 0.19±0.06. It remained unchanged during placebo 0.19±0.05 but increased to 0.22±0.05 (mean +20%) during iNO treatment (p=0.006, 95% CI for $aAPO_2$ difference: 0.01–0.06; Fig. 1, Table 1). The increase in $aAPO_2$ during iNO treatment was more pronounced in infants with a gestational age below 34 weeks (n=9, 95% CI for $aAPO_2$ difference: 0.006–0.08) than in more mature infants (n=6, 95% CI for $aAPO_2$ difference: –0.002 to 0.06).

Table 2 Comparison of values immediately before and after the intervention

	Before	Placebo	iNO 10 ppm	After
SPO_2 (%)	94±3	–	96±3	94±3
FIO_2	0.49±0.07	–	0.47±0.08	0.50±0.08
PaO_2 (kPa)	7.58±1.62	–	8.15±1.44	7.78±2.43
SPO_2 (%)	94±3	93±4	–	94±3
FIO_2	0.50±0.06	0.48±0.06	–	0.48±0.08
PaO_2 (kPa)	7.39±1.95	7.16±1.39	–	7.69±1.96

SPO_2 was 93±4% during placebo and 96±3% during iNO treatment (p<0.05), even though FIO_2 was reduced in some cases during iNO inhalation to avoid hyperoxygenation (Table 2). Respiratory rate, $PaCO_2$, mean arterial pressure, and heart rate remained unchanged during exposure to iNO or placebo (Table 1). Both NO concentration and CPAP pressure were kept stable (9.4±1.7 ppm and 4.4±0.4 cmH_2O, respectively). NO_2 concentration was 0.3±0.1 ppm. Methemoglobin values did not change significantly. No significant carry-over effects from the first treatment period was seen, although the statistical power testing carry-over effect was low, being afflicted with between-subject variation.

One patient experienced a suspected rebound reaction. The unblinded coinvestigator noted an immediate 2–3% decline in SPO_2, lasting 2–3 min after iNO was discontinued. At 72-h follow-up a total of five patients had received MV because of progressive RDS (n=4) or pneumothorax (n=1). Another patient suffered a minor pneumothorax that resolved without the need of MV. Four patients had received surfactant treatment. All patients eventually recovered completely, and no patient required supplemental oxygen at 30 days of age.

Discussion

This is the first controlled study of iNO administration in combination with nasal CPAP in spontaneously breathing preterm infants (gestational age at birth >27 weeks). We have found only a few prior case reports [15, 30]. Although the clinical relevance must be clarified in larger and longer trials, there was a statistically significant improvement in oxygenation in preterm infants with RDS when adding inhaled nitric oxide to nasal CPAP. Overall, the observed acute increase in $aAPO_2$ was moderate (mean 20%).

The dose of 10 ppm was chosen on the basis of previous work in mechanically ventilated preterm infants [31, 32, 33]. In our study $PaCO_2$ and respiratory rate remained unchanged throughout the study, suggesting that respiratory drive and ventilation in premature neonates are unaffected by iNO, when added or withdrawn. In addition, heart rate and invasively monitored arterial blood pressure showed insignificant variations during the study period. Thus there was no evidence of acute adverse effects on gas exchange, heart rate, or systemic blood pressure at the iNO dose (10 ppm) and time (30 min) used in our study.

We chose to study patients with moderate RDS and with a relative indication for exogenous surfactant to obtain a clearer picture of acute effects from adding NO. Only four patients were later considered in need of surfactant treatment with porcine surfactant (Curosurf, Chiesi, Italy).

Nine infants had a gestational age below 34 weeks, and they showed higher increase (mean 28%) in $aAPO_2$ upon iNO treatment than that seen in the more mature infants (mean 8%). These findings indicate that more immature infants benefit more from this type of treatment and are in line with our previous findings of an inverse relationship between gestational age and endogenous formation of NO in the upper airways of preterm infants [34]. Although endogenous upper airway NO production can be in the ppm range, preterm infants have only one-half the upper airway NO concentration of those born at term, with the lowest values immediately after birth [35]. Assuming that upper airway NO reach the lung by autoinhalation, the most immature infants may be the ones that have the greatest need of NO supplementation to achieve sustained pulmonary vasodilatation and optimal gas exchange after birth.

Desandes et al. [36] reported improved oxygenation in preterm RDS infants treated with iNO and MV. They also examined pulmonary artery pressure with echo Doppler and observed a clear rise in $aAPO_2$ only in the patients displaying a baseline elevation in pressure. We did not obtain data on this parameter in our study and cannot state to what extent exposure to iNO influenced pulmonary pressure. The responders to iNO may have had a higher degree of lung vascular constriction than patients with less or no change in oxygenation. In this study nasal CPAP pressure was kept constant as it has previously been shown in animals that positive airway pressure and lung recruitment are a necessary prerequisite in order for the nitric oxide mediated lowering of pulmonary artery pressure and selective steal mechanism to occur [16], thus influencing oxygenation. It is our opinion that the observed oxygenation improvement in itself cannot justify the addition of iNO to newborns during nCPAP treatment. However, as mentioned above, we have noted that recent work on iNO expands the pharmacodynamic effects of iNO beyond dilation of constricted lung vascular and possibly bronchial smooth muscle cells. Schreiber et al. [17] recently reported decreased mortality, with a tendency to less intracranial hemorrhage and less development of chronic lung disease in neonates given iNO for a prolonged time. Their patients having median oxygenation index less than 6.94 had the greatest effect from iNO, in Scandinavia these would be babies treated with nCPAP.

A future study should explore the combination of iNO and nCPAP with the aim of reducing the need for MV and intubation in RDS infants, as MV is thought to add to morbidity in such preterm infants with RDS [14]. We consider it necessary to first determine the feasibility of combining iNO with nCPAP in vivo in the short term and determine acute effects on oxygenation when iNO is added or discontinued. Furthermore, since these patients remain spontaneously breathing, we also considered it important to assess potential effects on respiratory drive since this has not previously been reported.

Ethical aspects

While this study was enrolling patients, we had access to iNO as an off-label compassionate option in the ICU, in the unlikely event that one of the study subjects during or just after completing the protocol would react with severe pulmonary hypertension with or without hypoxemia. In planning the study we decided against the option to continue with iNO in combination with nasal CPAP in the event that an infant had become markedly unstable. We would instead have considered intubation, start of MV,

surfactant, and iNO in that order. There was no delay in instituting surfactant therapy in our study; in the 4 of 15 infants who received surfactant the therapy was given several hours after completing the study protocol. Moreover, we did not aim to substitute surfactant replacement with the use of iNO in combination with nasal CPAP. On the contrary, we suggest that a future successful therapy algorithm include assisted ventilation in some form to recruit lung together with surfactant and the addition of iNO [15]. Experimental data suggest a better outcome in various types of lung injury from such a combination approach [19, 37].

Safety aspects

The performance of the delivery system for iNO was adequate, as predicted in our earlier study [15]. One infant reacted with a 3% drop in saturation upon discontinuation of study gas, which prompted the blinded investigator at the bedside to restart study gas for an additional period of a few minutes. As a result oxygenation improved and continued to be stable. The study gas at that time was iNO; thus active drug was restarted but could be withdrawn at a second attempt to wean. At follow-up no patient was receiving supplemental oxygen at 30 days of age. We consider the clinical complications to RDS suffered by these newborn infants to be representative for the natural course of the illness.

Limitations of the study

We studied only 15 neonates and administered iNO at one occasion for 30 min, focusing mainly on acute effects on circulation and gas exchange. Our experience is thus small, and our conclusions relevant only for acute effects of adding 10 ppm iNO in neonates treated with nCPAP for RDS at a time point when the use of surfactant has not yet been prescribed. The advantage of a limited exposure time was the possibility to perform a placebo-controlled blinded cross-over on a similar degree of mismatching (ventilation to perfusion) for each patient. An additional limitation was the lack of echocardiographic data on pulmonary vascular pressure and on patency of the ductus arteriosus before and during iNO. It is possible that neonates with elevated pulmonary vascular pressures and right-to-left ductal shunting had a proportionally greater response to iNO, as recently reported for intubated premature newborns [36]. The improved oxygen tension that we found in postductal blood, sampled from umbilical artery catheters, could fit into such an interpretation.

Conclusion

The addition of 10 ppm iNO results in a slight but statistically significant acute improvement in oxygenation in newborn preterm infants treated with nasal CPAP for moderate RDS. There was no alteration in respiratory drive as assessed by repeated measurement of arterial carbon dioxide tension and respiratory rate. During weaning from iNO we observed only a minor tendency to withdrawal reaction. No other adverse effects from exposure to iNO were noted. We suggest that outcome studies should focus on the possibility of reducing need for intubation and MV by combining surfactant and iNO with nCPAP [15] in preterm newborn infants with RDS, thereby possibly reducing the incidence of bronchopulmonary dysplasia.

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