RESUMEN.

Óxido nítrico en la hipoplasia pulmonar: Resultados del Centro de Registro Europeo de iNO

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Objetivos: El objetivo de este trabajo fue describir la respuesta al tratamiento y los datos de resultado para los recién nacidos prematuros con hipoplasia pulmonar tratados con óxido nítrico inhalado (NOI). Presumimos que una respuesta de oxigenación aguda a iNO estaría asociada con la supervivencia. Diseño: Se utilizó un diseño de estudio observacional retrospectivo para identificar casos de hipoplasia pulmonar en recién nacidos prematuros <34 semanas de gestación informados al Registro Europeo de iNO. Se recogieron datos demográficos y clínicos que incluyen oxigenación y parámetros ecocardiográficos. El resultado primario fue la respuesta de oxigenación aguda definida como una reducción en el oxígeno inspirado fraccional de> 0.15. Los datos de resultado incluyeron enfermedad pulmonar crónica (EPC) y muerte. RESULTADOS: Setenta y dos recién nacidos con hipoplasia pulmonar fueron tratados con iNO durante un período de 10 años (2007-2016). En total, 30/69 (43%) de los lactantes mostraron una mejora significativa en la oxigenación y fueron categorizados como "respondedores". Treinta y un bebés tratados murieron, y 19 sobrevivientes desarrollaron EPC. Aunque no hubo diferencias en la demografía y los parámetros cardiorrespiratorios basales entre los respondedores y los no respondedores, una respuesta aguda se asoció significativamente con la supervivencia. Ni la hipertensión pulmonar ni la fisiología PPHN (hipertensión pulmonar persistente del recién nacido) predijeron la respuesta aguda a iNO o supervivencia. CONCLUSIÓN: Aunque la respuesta de oxigenación aguda al tratamiento con iNO en la hipoplasia pulmonar es comparable a otros trastornos respiratorios en recién nacidos prematuros, la mortalidad en este grupo sigue siendo muy alta. Una respuesta aguda se asocia con la supervivencia y sugiere que se justifica un breve ensayo terapéutico de la terapia con iNO en esta población. Este estudio subraya el valor de los registros en la evaluación de terapias para trastornos neonatales raros, aunque deben reconocerse sus limitaciones.

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Nitric Oxide in Pulmonary Hypoplasia: Results from the European iNO Registry

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Abstract
Objectives: The aim of this work was to describe treatment response and outcome data for preterm infants with pulmonary hypoplasia treated with inhaled nitric oxide (iNO). We hypothesised that an acute oxygenation response to iNO would be associated with survival. ***Design:*** A retrospective observational study design was used to identify cases of pulmonary hypoplasia in preterm infants <34 weeks' gestation reported to the European iNO Registry. Demographic and clinical data were collected including oxygenation and echocardiographic parameters. The primary outcome was acute oxygenation response defined as a reduction in fractional inspired oxygen of >0.15. Outcome data included chronic lung disease (CLD) and death. ***Results:*** Seventy-two infants with pulmonary hypoplasia were treated with iNO during a 10-year period (2007–2016). In total, 30/69 (43%) of the infants showed a significant improvement in oxygenation and were categorised as "responders." Thirty-one treated infants died, and 19 survivors developed CLD. Although there were no differences in demographics and baseline cardiorespiratory parameters between responders and non-responders, an acute response was significantly associated with survival. Neither pulmonary hypertension nor PPHN (persistent pulmonary hypertension of the newborn) physiology predicted the acute response to iNO or survival. ***Conclusion:*** Although the acute oxygenation response to iNO therapy in pulmonary hypoplasia is comparable to other respiratory disorders in preterm infants, mortality in this group remains very high. An acute response is associated with survival and suggests that a short therapeutic trial of iNO therapy is warranted in this population. This study underscores the value of registries in evaluating therapies for rare neonatal disorders, although their limitations must be recognised.

Introduction

Pulmonary hypoplasia occurs when there is disruption to the co-ordinated process of lung development leading to impaired maturation and abnormal lung parenchyma with reduced ability for efficient gas exchange [1–3]. Causes include premature prolonged rupture of membranes (PPROM), oligohydramnios/anhydramnios, renal agenesis, congenital diaphragmatic hernia, neuromuscular problems, skeletal dysplasia, and space-occupying lesions of the chest. Pathophysiological changes to lung parenchyma and airways are associated with abnor-

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mal development of pulmonary vasculature, with increased pulmonary vascular resistance and elevated pulmonary arterial pressure [3].

Inhaled nitric oxide (iNO) is a selective pulmonary vasodilator used to treat hypoxic respiratory failure and pulmonary hypertension by lowering pulmonary vascular resistance and pulmonary artery pressure in addition to improving ventilation-perfusion matching. While iNO has become a well-established therapy in term and near-term neonates, its role in preterm infants remains controversial. Nevertheless, it is being used increasingly in this population [4].

Several small studies have studied the effects of iNO in preterm infants with PPROM and reported favourable outcomes with survival up to 100% [5–8]. However, these small studies are from single centres containing very few cases of PPROM complicated by pulmonary hypoplasia [9]. The aim of this study was to report treatment response and outcome data from a large cohort of preterm neonates diagnosed with pulmonary hypoplasia, treated with iNO, and entered into the European iNO Registry over a 10-year period.

Methods

The European iNO Registry, established in 2007, receives anonymised patient data on a voluntary basis from 43 NICU/PICU centres across 13 countries. Participating centres submit diagnostic, clinical, therapeutic, and outcome data on neonates treated with iNO using a secure, online portal (details at https://www.medscinet.net/ino/). There are no restrictions on patient management in centres with regard to local iNO therapy practices. The Registry is funded through charitable and commercial sources (see Funding Sources), its governance is overseen by a chairperson, steering group, and database administrator.

Our study had a retrospective observational cohort design using data submitted prospectively into the Registry. The database was searched identifying infants with a diagnosis of pulmonary hypoplasia, born at <34 weeks' gestation and who received iNO treatment. The diagnosis of pulmonary hypoplasia was made clinically at the discretion of the attending clinician and selected as an individual item from a list of pre-specified diagnoses. Cases of pulmonary hypoplasia complicated by congenital diaphragmatic hernia, neuromuscular disorders, and skeletal dysplasia were excluded. Data were collected on patient demographics, concomitant cardiorespiratory support, pretreatment clinical status, iNO treatment, response to iNO treatment, adverse reactions, and final outcomes. Baseline (pretreatment) echocardiographic assessment was performed according to local protocols and used to categorise the presence of pulmonary hypertension. Babies were further categorised into those with and without PPHN (persistent pulmonary hypertension of the newborn) physiology (defined as severe pulmonary hypertension complicated by right ventricular dysfunction and/or supra-systemic pulmonary arterial pressure resulting in right-to-left shunt at atrial or ductal levels).

Table 1. Patient characteristics

	Cases (n = 72)
BW, kg	1.21 (0.96–1.53)
GA, weeks	28 (26–30)
Male	56 (78)
High-frequency ventilation	48 (67)
Inotropes/pressors	41 (57)
Surfactant	67 (93)
IV vasodilator	3 (4)
Baseline echocardiogram	44 (61)
Evidence of pulmonary hypertension on echocardiogram	30 (68)
Evidence of PPHN physiology on echocardiogram	27 (61)

Values are shown as the median (IQR) or n (%). BW, birth weight; GA, gestational age; PPHN, persistent pulmonary hypertension of the newborn.

The primary outcome in this study was the short-term oxygenation response to iNO therapy. Our hypothesis was that an early response to iNO would be associated with medium- to long-term outcomes, including chronic lung disease (CLD) and survival to hospital discharge. Additionally, we hypothesised that early response and survival would be associated with the presence of PPHN physiology on baseline echocardiography. Furthermore, we aimed to describe the response rates and demographics of preterm babies with pulmonary hypoplasia treated with iNO.

Early response was assessed by comparing respiratory parameters before and 30–60 min after starting treatment. An improvement in oxygenation, demonstrated by a reduction in the fractional inspired oxygen concentration (FiO_2) of 0.15 or more, was used to define a positive response. We compared patient demographics, cardiorespiratory parameters, and final outcomes in responders and non-responders. CLD was defined as oxygen dependency or respiratory support at 36 weeks' postmenstrual age and information was collected about death prior to hospital discharge, including the cause of death.

The Mann-Whitney U test and χ^2 tests were used for continuous and categorical data, respectively, and the Wilcoxon signed-rank test was used for related samples. Data analyses were carried out using SPSS Statistics version 22 (IBM Corporation). In this multicentre, multinational European study each site followed local requirements for the submission of data to the Registry and for use of the anonymised data in research studies. No further ethics review was needed.

Results

Seventy-two infants with pulmonary hypoplasia treated with iNO were identified from the European iNO Registry database between January 2007 and December 2016. The patient characteristics are outlined in Table 1. The major-

Table 2. Short-term oxygenation response to iNO

	Pre-iNO	Post-iNO	*p* value
FiO_2	1 (0.9–1)	0.83 (0.5–1)	<0.001
PaO_2, mm Hg	35 (24–46)	50 (37–71)	<0.001
MAP, cm H_2O	14 (13–18)	16 (13–18)	0.19
OI	41.9 (25.2–59.9)	18.2 (11.9–34)	<0.001

Values are shown as the median (IQR). There were 69/72 infants in whom the oxygenation response could be calculated. MAP, mean airway pressure; OI, oxygenation index.

ity of babies were receiving advanced cardiorespiratory support before iNO therapy was started, including surfactant, high-frequency ventilation, and inotropes/pressors.

Forty-four infants had an echocardiogram prior to starting iNO treatment; 30 (68%) had evidence of pulmonary hypertension and 27 (61%) had evidence of PPHN physiology. iNO started at a median age of 4 h (IQR 2–9) and continued for a median duration of 55 h (IQR 22–99). The median starting dose of iNO was 20 ppm (IQR 10–20) with a median maintenance dose of 17 ppm (IQR 10–20). The maximum dose was no greater than 20 ppm.

Table 2 summarises the acute oxygenation response to iNO. A significant decrease in FiO_2 and increase in PaO_2 corresponded to a decrease in the median oxygenation index (OI) from 41.9 to 18.2 within 60 min of starting iNO; however, there was considerable inter-individual variation (Fig. 1). Overall, 31/72 (43%) babies died and, of the survivors, 19 (46%) were oxygen dependent at 36 weeks' postmenstrual age. For comparison, the mortality rate in iNO-treated babies without pulmonary hypoplasia entered into the Registry was 42%.

Data were available to classify 69 infants as responders ($n = 30$) or non-responders ($n = 39$); information on FiO_2 was incomplete in 3 babies. Forty-three percent of babies showed an acute response to iNO. Responders and non-responders were broadly comparable by gestational age and birth weight, as well as pretreatment oxygenation and cardiorespiratory support parameters; responders and non-responders did not differ significantly in baseline oxygenation parameters and ventilatory support. There was no significant difference in the proportion of babies with echocardiographic evidence of pulmonary hypertension/PPHN physiology, which was present in approximately two-thirds of the babies.

The response to iNO therapy predicted the final outcome (Table 3): an acute oxygenation response to iNO was associated with a significantly lower risk of death (OR

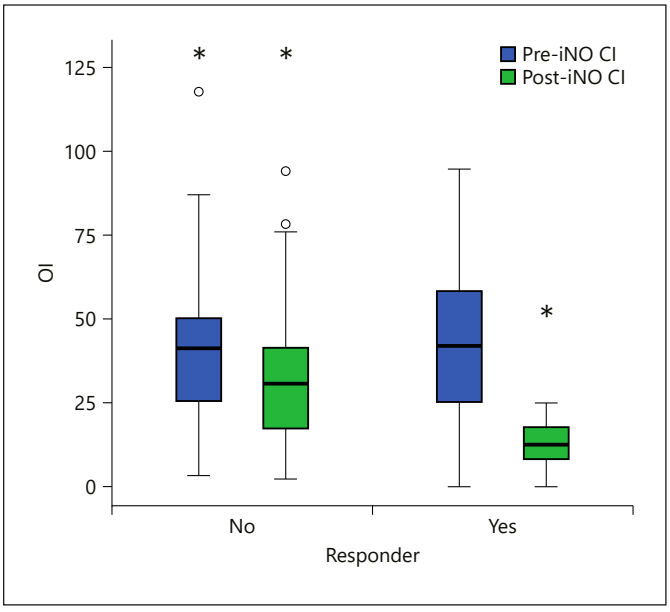

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Fig. 1. Pre- and post-iNO treatment OI in responders and non-responders.

0.18, 95% CI 0.06–0.55). The response to iNO was not associated with a reduction in CLD. Neither pulmonary hypertension nor PPHN physiology predicted survival: 15 babies with pulmonary hypertension died and 15 survived ($p = 0.68$); 14 babies with PPHN physiology died and 13 survived ($p = 0.37$). Baseline cranial ultrasonography was available prior to iNO therapy in 28 babies (24 no IVH, 2 grade 1, 1 grade 2, and 1 grade 3), and final cranial ultrasound status was available in 54 babies (32 no IVH, 10 grade 1, 5 grade 2, 3 grade 3, and 4 grade 4).

Of the 31 (43%) infants who died, pulmonary hypoplasia/respiratory distress was the cause of death in 22 infants, cardiorespiratory failure was the cause in 4 infants, intracranial haemorrhage was responsible in 2 infants, and necrotising enterocolitis, renal failure, and sepsis in 1 infant each. Only 4 adverse events were reported in this cohort. There were 2 cases complicated by pulmonary haemorrhage: 1 baby developed rebound hypoxaemia after discontinuing iNO and the last baby developed a tension pneumothorax whilst receiving iNO.

Discussion

This study describes short- and longer-term outcomes in babies with pulmonary hypoplasia treated with iNO and, to our knowledge, represents the largest reported

Table 3. Characteristics of responders and non-responders

	Responders (n = 30)	Non-responders (n = 39)	p value
GA, weeks	28 (26–30)	28 (26–30)	0.61
BW, kg	1.21 (0.95–1.59)	1.2 (0.95–1.45)	0.61
Baseline OI	41.9 (23.6–59.9)	41.2 (25–50.5)	0.90
Baseline FiO_2	1 (0.9–1)	1 (1–1)	0.29
Baseline PaO_2, mm Hg	33 (26–44)	37 (23–47)	0.56
Baseline MAP, cm H_2O	13.5 (12–17.25)	15 (13–18)	0.13
HFOV	18 (60)	27 (68)	0.43
Pulmonary hypertension[1]	11 (65)	18 (69)	0.63
PPHN physiology[1]	10 (58)	16 (62)	0.71
BPD	9 (30)	9 (23)	0.47
Death	6 (20)	23 (59)	0.007

Values are shown as the median (IQR) or n (%). Three babies were excluded in whom oxygenation data were incomplete. GA, gestational age; BW, birth weight; OI, oxygenation index; HFOV, high-frequency oscillatory ventilation; PPHN, persistent pulmonary hypertension of the newborn; BPD, bronchopulmonary dysplasia.

[1] Of those that had a baseline echocardiogram.

European cohort of such babies. Approximately only 40% of babies with pulmonary hypoplasia responded to iNO with improved oxygenation within 1 h of starting therapy. The overall response rate is comparable to previously reported studies of iNO used to treat hypoxaemic respiratory failure in preterm and term babies [10–12]. However, much higher response rates were reported in a recent overview of studies describing iNO use in babies born following PPROM, with 94% of treated babies showing a short-term response in oxygenation [2].

The survival in our cohort was 57%, much lower than in potentially comparable studies which reported survival rates of between 83 and 87% [2, 7, 13]. However, these studies principally reported outcomes in babies with PPROM containing very few babies diagnosed with pulmonary hypoplasia. In the largest study published to date of iNO-treated infants with pulmonary hypoplasia, Ellsworth et al. [14] reported a lower survival rate of 59%, almost identical to this study, but no association between iNO exposure and survival.

Differences between our findings and some of the previous studies in respect of oxygenation response and survival might be explained by several factors, including case mix and publication bias. Our study population comprised infants whose data were submitted voluntarily to the Registry by various neonatal centres throughout Europe. Although not a protocolised clinical trial, a standardised dataset was collected for each baby. Almost all other similar studies have reported outcomes in relatively small case series from single centres. Risk of publication bias with selective publication of case series with positive findings is well recognised and may explain why previously published papers are almost universally supportive of iNO therapy in apparently similar populations [14]. We believe that these results from a non-selected population offer some balance to the debate of the value and efficacy of iNO in these babies.

Other similar studies have included all babies with PPROM inferring that the majority would have pulmonary hypoplasia. However, in a recent study only 23% of babies born following early PPROM (before 24 weeks' gestation) developed pulmonary hypoplasia [15]. Our study population only included babies with a clinical diagnosis of pulmonary hypoplasia and is likely to represent a group with a higher baseline mortality risk than those in other studies. Acute oxygenation response in this cohort predicted longer-term outcome with respect to survival. iNO responsiveness has been shown to be associated with improved clinical outcomes in other recent studies [12, 16]. Despite a lack of RCT evidence of efficacy in preterm infants [11], some expert groups recommend that iNO should be considered for treatment of severe hypoxaemia in preterm infants in the context of PPHN physiology, particularly if associated with prolonged rupture of membranes and oligohydramnios [17–20].

Our findings support a therapeutic trial of iNO in preterm infants with pulmonary hypoplasia. In this study,

echocardiographically confirmed pulmonary hypertension/PPHN was not associated with an acute response to iNO and did not predict survival. Similarly, both Ellsworth et al. [14] and Carey et al. [21] found no significant association between iNO exposure and mortality in preterm infants with pulmonary hypoplasia/PPHN and respiratory distress syndrome/PPHN, although PPHN was not echocardiographically defined.

This study underscores the value of large datasets for investigating the safety and efficacy of therapies in relatively rare conditions such as pulmonary hypoplasia. High-quality patient registries are well established with proven worth in other paediatric disorders such as pulmonary arterial hypertension [22]. Although few similar registries exist in neonatal critical care, the potential value of a multicentre registry for iNO therapy in preterm infants has been recognised [18] and a recent review specifically recommended establishing a clinical register to collect data on infants born after PPROM [2]. The European iNO Registry data also provide information on the safety of iNO. This study identified 2 cases of pulmonary haemorrhage in 72 infants (2.8%) which, despite being an accepted adverse effect, has rarely been reported [13]. Large registry-based datasets allow such rare adverse effects of therapy to be quantified.

As with other studies [6, 14], we acknowledge that the principal limitation of our study is the lack of a standardised definition of pulmonary hypoplasia, relying on individual clinicians diagnosing pulmonary hypoplasia clinically. The gold standard pathological definition is based on quantitative and/or qualitative underdevelopment of bronchial or pulmonary components of the lung characterised by lung weight, lung/body weight ratio, or lung DNA content [23, 24]. The clinical definition of pulmonary hypoplasia includes early-onset respiratory failure supported by radiographic findings of low-volume lungs, elevated hemi-diaphragms, and a bell-shaped thorax. Although pulmonary hypoplasia might be the consequence of various underlying diagnoses, we excluded these, meaning cases of pulmonary hypoplasia included in this study were likely to be oligohydramnios either from PPROM or renal agenesis.

A further limitation is the absence of a control group. By definition, the Registry contains data on babies treated with iNO and, therefore, cannot provide information on similar babies who did not receive iNO. The study was not designed to answer the question of whether or not iNO improves outcome in preterm infants with pulmonary hypoplasia; this would require an adequately powered randomised controlled trial.

Conclusion

Although an acute oxygenation response to iNO therapy in pulmonary hypoplasia is comparable to other respiratory disorders in preterm infants, mortality in this group remains very high. An acute response is associated with survival and supports our view that a short therapeutic trial of iNO therapy is reasonable in this population. This study underscores the value of registries in evaluating therapies for rare neonatal disorders.

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Statement of Ethics

In this multicentre, multinational European study each site followed local requirements for the submission of data to the Registry, and use of the anonymised data in research studies. No further ethics review was required.

Disclosure Statement

Dr. Nimish V. Subhedar chairs the European iNO Registry which receives financial support from charitable and commercial sponsors, the Liverpool Women's Hospital Newborn Appeal Charity, Linde Healthcare, and the SOL Group; none of these organisations had a role in study design, data collection/analysis/interpretation, or manuscript preparation.

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Author Contributions

N.V.S. developed the project idea. R.K. was responsible for data collection and analysis. Both N.V.S. and R.K. contributed to data interpretation and writing the manuscript.

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