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# Inhaled nitric oxide (iNO) for preventing prematurity-related bronchopulmonary dysplasia (BPD): 7-year follow-up of the European Union Nitric Oxide (EUNO) trial

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## Abstract

**Objectives:** Most studies of inhaled nitric oxide (iNO) for prevention of bronchopulmonary dysplasia (BPD) in premature infants have focused on short-term mortality and morbidity. Our aim was to determine the long-term effects of iNO.

**Methods:** A 7-year follow-up was undertaken of infants entered into a multicenter, double-blind, randomized, placebo-controlled trial of iNO for prevention of BPD in premature infants born between 24 and 28 weeks plus six days of gestation. At 7 years, survival and hospital admissions since the 2-year follow-up, home oxygen therapy in the past year, therapies used in the previous month and growth assessments were determined. Questionnaires were used to compare general health, well-being, and quality of life.

**Results:** A total of 305 children were assessed. No deaths were reported. Rates of hospitalization for respiratory problems (6.6 vs. 10.5%, iNO and placebo group, respectively) and use of respiratory medications (6.6 vs. 9.2%) were similar. Two patients who received iNO and one who received placebo had received home oxygen therapy. There were no significant differences in any questionnaire-documented health outcomes.

**Conclusions:** iNO for prevention of BPD in very premature infants with respiratory distress did not result in long-term benefits or adverse long-term sequelae. In the light of current evidence, routine use of iNO cannot be recommended for prevention of BPD in preterm infants.

**Keywords:** bronchopulmonary dysplasia (BPD); inhaled nitric oxide; long-term outcomes.

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## Introduction

Bronchopulmonary dysplasia (BPD), which results in severe respiratory distress in premature infants, is associated with increased mortality, pulmonary hypertension, reduced lung function, increased airway obstruction, poor growth, and neurodevelopmental problems later in life [1–3]. Inhaled nitric oxide (iNO) is indicated to improve oxygenation and reduce the need for extracorporeal membrane oxygenation in term and near-term infants (>34 weeks' gestation) with hypoxic respiratory failure associated with pulmonary hypertension [4]. While some prospective studies of iNO for prevention or treatment of BPD in preterm infants with severe respiratory failure have shown a benefit [5–7], most have not [8–14]. Most research regarding iNO for BPD prevention has focused on the short-term pathogenesis and prevention during the early neonatal period, rather than on long-term sequelae [1]. As with the original short-term studies, longer-term studies of iNO for prevention of BPD-related outcomes in patients 1–5 years old have also

yielded mixed results with regard to mortality, abnormal neurodevelopment, and medication use [15–21].

Primary results from the European Union Nitric Oxide (EUNO) study showed that iNO (INOMax®; Mallinckrodt Pharmaceuticals, Bedminster, NJ, USA) administered for prevention of BPD provided no improvement in survival without BPD at 36 weeks in preterm neonates born between 24 and 28 weeks plus 6 days gestational age with mild-to-moderate respiratory distress syndrome (RDS) compared with placebo (66 vs. 65%, respectively, alive without BPD at 36 weeks' postmenstrual age) [12]. A follow-up study of the patients who had survived to 1 and 2 years of age showed no significant between-group difference in growth, neurological development or respiratory outcomes [20]. There have been no studies assessing outcomes of iNO usage after 5 years of age. Our aim was to assess the long-term effects of iNO usage at 7 years of age.

## Materials and methods

### Study design and patients

We assessed children who had been entered into the EUNO trial, which was a multicenter, double-blind, randomized, placebo-controlled study conducted in nine countries in the European Union (ClinicalTrials.gov Identifier: NCT00551642). The design has been described in detail previously [12] and is summarized here briefly. Infants born between 24 and 28 weeks plus 6 days of gestation, weighing  $\geq 500$  g and requiring surfactant within 24 h of birth (prophylactically or for signs of developing respiratory distress), or continuous positive airway pressure (CPAP) (fraction of inspired oxygen  $\geq 0.3$  on mean airway pressure of  $\geq 4$  cm water) within 24 h to maintain an oxygen saturation of at least 85%, were eligible for the study.

Patients were randomized one:one to iNO (5 ppm) or placebo (nitrogen gas) and stratified by study site and gestational age (24–25 weeks plus 6 days and 26–28 weeks plus 6 days). Treatment was initiated within 2 h of eligibility and no later than 26 h of life and was continued for at least 7 days, up to a maximum of 21 days. Study gas was administered via an INOvent drug delivery system inserted into the patient's breathing circuit [12].

### Assessment and endpoints

The 7-year follow-up was conducted by a member of the investigators' staff blinded to the group assignment. The outcomes were survival status and hospital admission since the 2-year follow-up, home oxygen therapy in the past year, therapies used in the month before the 7-year visit and vital signs, physical examination and growth assessment results. In addition, the Strengths and Difficulties Questionnaire (SDQ) and the Health Utilities Index (HUI) questionnaire were used to compare general health and well-being and quality of life between the iNO and placebo groups. The SDQ comprises 25 questions in five domains: emotional problems,

conduct problems, hyperactivity, peer problems, and prosocial behavior, as well as a total difficulties scale [22]. Total scores on the subscales range from zero to 10, with the total difficulties score ranging from zero to 40 (the prosocial domain is not incorporated into the total difficulties score) [22]. The HUI questionnaire contains 18 questions that were used to create the HUI2, which has six attributes, sensation, mobility, emotion, cognition, self-care and pain, and the HUI3, which has eight attributes, vision, hearing, speech, ambulation, dexterity, emotion, cognition, and pain [23]. Each attribute is scored on a four-, five-, or six-point scale, with higher scores indicating worse conditions. These scores were converted to single-attribute utility scores, with zero indicating most disabled and one indicating no disability. Based on the attribute levels of HUI2 and HUI3, two-level disability categories of none/mild and moderate/severe were created. The HUI2 and HUI3 health status classification system and utility scoring functions were used to develop a Health-Related Quality of Life (HRQOL) multi-attribute utility score, with values ranging from zero (dead) to one (healthy) [24].

### Data analysis

The analysis population for the 7-year follow-up included all patients who received the study treatment (iNO or placebo) and had a completed 7-year case report form. No missing data imputation was performed. Comparisons between iNO and placebo were made using *t* tests for continuous variables and Fisher exact test for categorical variables. All statistical tests were two-sided at a significance level of 0.05.

Data were collected on a pre-designed case report form and entered into an Oracle Clinical database using a double-entry method and then converted to an internally validated SAS database for analysis. All analyses were conducted using SAS version 9.2 or higher.

### Ethics

The study was approved by the appropriate regulatory authority in each country, and by the local Research Ethics Committee at each institution [12]. Informed consent for participation was obtained from parents.

## Results

### Baseline characteristics

Of the 702 patients who survived to 36 weeks gestational age across the 35 study sites participating in the primary study, 305 from 24 sites were assessed at the 7-year follow-up (iNO,  $n=152/305$  [49.8%]; placebo,  $n=153/305$  [50.2%]) (Figure 1). A total of 397/702 (56.6%) original survivors were lost to 7-year follow-up; 209/702 (29.8%) because their study sites ( $n=11$ ) discontinued study participation prior to the 7-year assessments and 188/702 (26.8%) across the 24 study sites that continued participation in the study through the 7-year follow-up. Baseline characteristics and major morbidities

during the first hospitalization of patients in the 7-year follow-up cohorts are shown in Table 1. Characteristics of the cohort included in the current analysis were similar to those of patients in the original EUNO study [12].

## Survival and other outcomes

There were no deaths reported from the end of the 2-year follow-up to the 7-year follow-up. Overall, rates of hospitalizations during this period were 28.9% and 34.6% in the iNO and placebo groups, respectively ( $p=0.29$ ), with 6.6% of patients hospitalized for respiratory/breathing difficulties in the iNO group compared to 10.5% in the placebo group ( $p=0.23$ ; Table 2). Growth assessment results were comparable in the study groups. The mean (standard deviation [SD]) weight was 23.0 (6.78) kg and 22.6 (4.63) kg in the iNO and placebo groups ( $p=0.58$ ), respectively; mean (SD) length was 121.3 (6.15) cm and 120.6 (6.40) cm ( $p=0.35$ ), respectively. There were no significant differences in physical examination results (Supplementary Table 1).

## Therapies and medications

Two (1.3%) patients in the iNO group and one (0.7%) in the placebo group received home oxygen therapy during the year prior to the 7-year follow-up ( $p=0.56$ ). Overall, 20% of patients were receiving supportive therapy, with no difference between the study groups ( $p=0.86$ ). Twelve (7.9%) patients in the iNO group and nine (5.9%) in the placebo group were receiving speech therapy ( $p=0.49$ ), and 15 (9.9%) and nine (5.9%), respectively, were receiving physical therapy

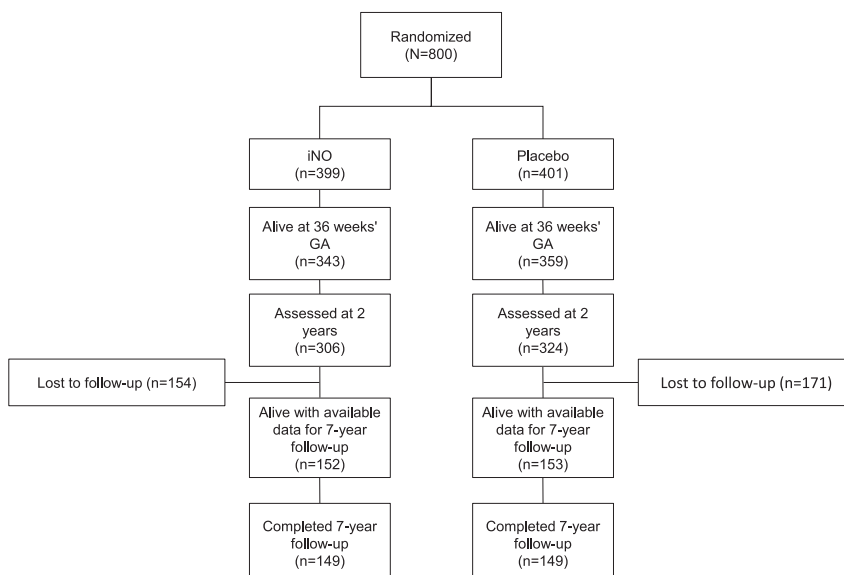
**Table 1:** Baseline characteristics during the first hospitalization.

Variable	Inhaled nitric oxide (n=152)	Placebo (n=153)
Gestational age at birth, mean (SD), weeks	26.6 (1.16)	26.5 (1.35)
<26 weeks, n (%)	39 (25.7)	54 (35.3)
≥26 weeks, n (%)	113 (74.3)	99 (64.7)
Birth weight, mean (SD), g	870.2 (197.34)	885.3 (188.24)
Birth length, mean (SD), cm	34.1 (2.82) <sup>a</sup>	33.9 (3.07) <sup>b</sup>
Male sex, n (%)	75 (49.3)	83 (54.2)
Mother's race <sup>c</sup> , n (%)		
White	125 (82.2)	137 (89.5)
Black	14 (9.2)	10 (6.5)
Other	13 (8.6)	6 (3.9)
5-min Apgar score, median (range)	8.0 (2.0, 10.0) <sup>d</sup>	8.0 (0, 10) <sup>e</sup>
Exposure to study drug, mean (SD), days	17.6 (5.49)	17.9 (5.47)

<sup>a</sup>n=125. <sup>b</sup>n=127. <sup>c</sup>Self-reported by the parents of the patient. <sup>d</sup>n=147. <sup>e</sup>n=150.

( $p=0.20$ ). Seven (4.6%) patients in the iNO group and 15 (9.8%) in the placebo group were receiving some other therapy (i.e., not speech or physical therapy) ( $p=0.08$ ).

Proportions of patients taking respiratory medications were similar in both study groups. Ten patients (6.6%) randomized to iNO and 14 (9.2%) randomized to placebo were currently taking respiratory medications at the 7-year follow-up ( $p=0.40$ ). The most commonly used respiratory medications were inhaled corticosteroids (six iNO patients [3.9%] and 11 placebo patients [7.2%];  $p=0.22$ ), and  $\beta_2$ -adrenergic receptor agonists (five iNO patients [3.3%] and eight [5.2%] placebo patients, respectively;  $p=0.40$ ). Seventeen patients (11.2%)



**Figure 1:** Patient disposition. GA, gestational age; iNO, inhaled nitric oxide.

**Table 2:** In-hospital admissions between 2- and 7-year follow-up.

Category	Inhaled nitric oxide (n=152)	Placebo (n=153)	p-Value
Admitted to hospital since the 2-year visit	44 (28.9)	53 (34.6)	0.29
Hospitalized for respiratory/breathing difficulties	10 (6.6)	16 (10.5)	0.22
Hospitalized for surgery	33 (21.7)	32 (20.9)	0.87
Hospitalized for other reason	14 (9.2)	16 (10.5)	0.72
Admitted to ICU	6 (3.9)	3 (2.0)	0.31
Required mechanical ventilation	4 (2.6)	2 (1.3)	0.41

Data are shown as n (%); ICU, intensive care unit.

and 15 (9.8%) in the iNO and placebo groups, respectively, were receiving non-respiratory medications ( $p=0.69$ ).

## Health outcomes questionnaires

Results of the SDQ were generally similar in the placebo and iNO groups overall and with regard to conduct problems, hyperactivity and prosocial scales (Table 3). There were no significant differences in the emotional problems category (125/147 [85.0%] vs. 113/147 [76.9%];  $p=0.10$ ). HUI2 and HUI3 results were similar in both groups for all attributes (Table 4).

## Discussion

This study demonstrated that iNO had no significant effect on mortality, growth, hospitalization, outpatient therapy, medication use, HRQOL and overall health outcomes at 7 years of follow-up in premature infants. The current data set represents the longest duration of neurodevelopmental follow-up to date in patients treated with iNO for prevention of BPD and its consequences.

There have been a number of studies assessing long-term outcomes from randomized controlled studies of iNO, but they have usually been when the participants have been at one to two years of corrected age. Several studies have shown that neurodevelopmental outcome is not adversely affected by iNO [15, 18] but only one showed that it has been improved at approximately two years of age [19]. In this one, a single-center trial, adverse neurodevelopmental outcomes were lower in the iNO-treated group vs. placebo (24 vs. 46%) [19]. All of those studies used a higher dose of iNO than in the trial for which we report the 7-year follow-up. A Cochrane review published in 2017 demonstrated no significant impact of iNO on neurodevelopment impairment [25].

**Table 3:** Strengths and Difficulties Questionnaire (SDQ) results for patients with 7 year follow-up data.

Category	Inhaled nitric oxide (n=147)	Placebo (n=147)	p-Value
Emotional problems scale <sup>a</sup>	1.9 (1.79)	2.1 (1.96)	0.24
Conduct problems scale <sup>b</sup>	1.4 (1.55)	1.4 (1.58)	1.00
Hyperactivity scale <sup>c</sup>	3.8 (2.64)	3.4 (2.66)	0.30
Peer problems scale <sup>b</sup>	1.2 (1.41)	1.5 (1.74)	0.13
Prosocial scale <sup>d</sup>	8.6 (1.73)	8.4 (1.81)	0.25
Total difficulties scale <sup>e</sup>	8.3 (5.04)	8.5 (5.76)	0.72

Data are shown as mean (SD). <sup>a</sup>0–3 is normal; 4 is borderline; 5–10 is abnormal. <sup>b</sup>0–2 is normal; 3 is borderline; 4–10 is abnormal. <sup>c</sup>0–5 is normal; 6 is borderline; 7–10 is abnormal. <sup>d</sup>6–10 is normal; 5 is borderline; 0–4 is abnormal. <sup>e</sup>0–13 is normal; 14–16 is borderline; 17–40 is abnormal.

**Table 4:** Summary of Health Utility Index Mark 2 (HUI2) and Mark 3 (HUI3) single-attribute scores.

Attribute	Inhaled nitric oxide (n=152)	Placebo (n=153)	p-Value
HUI2			
Sensation	0.9 (0.17) <sup>a</sup>	0.9 (0.16) <sup>b</sup>	0.97
Mobility	1.0 (0.14) <sup>c</sup>	1.0 (0.08) <sup>d</sup>	0.39
Emotion	1.0 (0.08) <sup>b</sup>	1.0 (0.09) <sup>e</sup>	0.84
Cognition	1.0 (0.13) <sup>e</sup>	1.0 (0.13) <sup>d</sup>	0.87
Self-care	1.0 (0.20) <sup>b</sup>	1.0 (0.12) <sup>d</sup>	0.18
Pain	1.0 (0.05) <sup>b</sup>	1.0 (0.03) <sup>b</sup>	0.07
HUI3			
Vision	1.0 (0.14) <sup>c</sup>	1.0 (0.06) <sup>d</sup>	0.22
Hearing	1.0 (0.07) <sup>e</sup>	1.0 (0.03) <sup>d</sup>	0.17
Speech	1.0 (0.14) <sup>c</sup>	1.0 (0.14) <sup>b</sup>	0.90
Ambulation	1.0 (0.15) <sup>c</sup>	1.0 (0.11) <sup>d</sup>	0.55
Dexterity	1.0 (0.13) <sup>b</sup>	1.0 (0.07) <sup>d</sup>	0.22
Emotion	1.0 (0.02) <sup>b</sup>	1.0 (0.02) <sup>b</sup>	0.83
Cognition	0.9 (0.15) <sup>e</sup>	0.9 (0.17) <sup>d</sup>	0.96
Pain	1.0 (0.07) <sup>b</sup>	1.0 (0.07) <sup>d</sup>	0.44

Data are shown as mean (SD); higher attribute scores indicate worse conditions. <sup>a</sup>n=144. <sup>b</sup>n=147. <sup>c</sup>n=146. <sup>d</sup>n=148. <sup>e</sup>n=145.

Longer follow-up studies have been carried out. For example, following the INNOVO trial, at 4–5 years of age there was no significant difference in the results of cognitive and behavioral assessments with iNO vs. controls [21]. Two studies have looked at school-aged children. One assessing children at a mean age of 5.7 years from a single-center randomized controlled trial demonstrated no significant differences in school readiness, growth parameters or need for subsequent hospitalization, but a ( $p=0.05$ ) reduction in technology dependence and functional disability [26]. In a single-center follow-up study of children at 7–9 years of age

from the multicenter randomized controlled NO CLD study, no significant differences were found in pulmonary function or exercise capacity, with 63% of survivors followed up [27].

The current study population was 86% Caucasian and only 8% black. It has been suggested that white patients may be less likely to benefit from iNO treatment than black patients [5, 8]. A recent meta-analysis of trials that provided data according to race, reported by Askie and colleagues [28], found that African American infants had a statistically significant reduction in risk of BPD or death at 36 weeks following iNO treatment ( $p=0.003$ ), but that white and Hispanic infants did not. It should, however, be noted that the meta-analysis assumed that black infants were African American and did not provide information on whether or how race was determined beyond maternal self-report, nor did it assess long-term outcomes. A recent retrospective study [29] of iNO in a large cohort of premature African American ( $n=356$ ), white ( $n=502$ ), and Hispanic ( $n=258$ ) neonates did not corroborate the results reported by Askie and colleagues [28]. The complexity of the association between race/ethnicity and BPD risk is highlighted by the results of a genome-wide association study of iNO in 387 high-risk preterm infants [30]. In that study, improved survival without BPD in iNO-treated infants was seen in self-reported Hispanic white mothers, but not self-reported black/African American mothers.

The iNO trials conducted to date in preterm infants have included a range of patient populations (gestational ages ranging from 24–28 weeks to <34 weeks) and different strategies (initiation of iNO at different times after birth and duration of iNO administration), making it difficult to interpret overall study results [5–14]. Small for gestational age infants are at high risk of adverse outcomes including severe BPD [31], increased rehospitalization, and need for chest medications at follow-up [32]. There is no evidence, however, from randomized controlled trials that iNO will particularly benefit this group. Retrospective evidence suggests that prematurely born infants with premature and prolonged rupture of the membranes with severe hypoxic respiratory failure may be a targeted group for iNO therapy [33]. Aside from race, as mentioned above, it is unclear whether a particular patient population or specific iNO dosing or other treatment strategy may predict a better response to iNO in the short term, and if any of these factors would impact the long-term benefit.

This study has strengths and some limitations. This is the first study to assess the outcomes of very prematurely born infants at 7 years of age who had been entered into a neonatal randomized trial of iNO. We were able to assess 305 children and thus another strength of our study was that we report the 7-year outcomes of a large number of children who

were all born before 29 weeks of gestation. Unfortunately, 11 of the original 35 study centers did not participate in the 7-year follow-up. Nevertheless, the iNO and placebo groups were well balanced, with characteristics similar to those of the original randomized population [12]. This suggests that the results of our study reflect the overall population. Furthermore, there was not an unbalanced bias in the 2-year follow-up between the two groups iNO vs. placebo [20]. In addition, in the current 7-year follow-up study that was still blinded, the significant loss to follow-up came from the decision of 11 centers not to pursue the long-term follow-up, because of both lack of interest and funding. Therefore, although we cannot prove it, it is very unlikely there would be an unbalanced introduced factor between the two groups.

A criticism of our trial is that a proportion of the population was not intubated, and hence they may not have received sufficient iNO. In a randomized prospective, double-blind, crossover trial of administering iNO to preterm infants on CPAP for RDS, a significant improvement in oxygenation was seen suggesting that iNO can be delivered effectively non-invasively [34].

In conclusion, there were no meaningful between-group differences observed for any assessments conducted during the 7-year follow-up period. iNO for prevention of BPD in infants with respiratory distress born at 24–28 weeks and 6 days gestational age was then not associated with improved long-term outcomes or adverse effects. In the light of current evidence, routine use of iNO cannot be recommended for prevention of BPD in preterm infants.

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**Author contributions:** VPC conceptualized and designed the study, served as study investigator, and enrolled patients; FD served as study investigator, enrolled patients, and collected data; DF served as principal investigator and study investigator, enrolled patients, and collected, analyzed, and interpreted data; AG served as study investigator; MH served as study investigator, enrolled patients, and collected, analyzed, and interpreted data; HDH conceptualized and designed the study, served as principal investigator and study investigator, enrolled patients, and collected, analyzed, and interpreted data; BJ served as principal investigator and study investigator, enrolled patients, and analyzed and interpreted



data; JCM conceptualized and designed the study and served as principal investigator; JLP collected, analyzed, and interpreted data; and MSL conceptualized and designed the study, enrolled patients, and served as study investigator. All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

**Competing interests:** AG has held grants from and has received honoraria for giving lectures and advising, various manufacturers (Abbott Laboratories, MedImmune) and ventilator manufacturers (SLE). She is currently receiving a nonconditional educational grant from SLE. JLP is an employee of Mallinckrodt Pharmaceuticals and may hold stock or stock options in that company. The other authors have no conflicts of interest relevant to this article to disclose.

**Clinical trial registration number and registry name:** ClinicalTrials.gov Identifier: NCT00551642. Safety and efficacy study of nitric oxide for inhalation on chronic lung disease in premature babies.

**Data sharing statement:** The datasets generated and analyzed for this manuscript are not publicly available. Primary data for this study can be found at <https://clinicaltrials.gov> (ClinicalTrials.gov Identifier: NCT00551642). Requests for additional information should be made to the corresponding author.

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