Multicenter Randomized Controlled Trial of Inhaled Nitric Oxide for Pediatric Acute Respiratory Distress Syndrome

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Objectives To test the hypothesis that inhaled nitric oxide (iNO) would lead to improved oxygenation and a decrease in duration of mechanical ventilation in pediatric patients with acute respiratory distress syndrome.

Study design A total of 55 children with acute respiratory distress syndrome were enrolled from 9 centers. Patients were randomized to iNO or placebo and remained on the study drug until death, they were free of ventilator support, or day 28 after the initiation of therapy.

Results Mean baseline oxygenation indexes (OIs) were 22.0 ± 18.4 and 25.6 ± 14.9 (iNO and placebo groups, respectively, $P = .27$). There was a trend toward an improved OI in the iNO group compared with the placebo group at 4 hours that became significant at 12 hours. There was no difference in the OI between groups at 24 hours. Days alive and ventilator free at 28 days was greater in the iNO group, 14.2 ± 8.1 and 9.1 ± 9.5 days (iNO and placebo groups, respectively, $P = .05$). Although overall survival at 28 days failed to reach statistical significance, 92% (22 of 24) in the iNO group and 72% (21 of 29) in the placebo group ($P = .07$), the rate of extracorporeal membrane oxygenation–free survival was significantly greater in those randomized to iNO 92% (22 of 24) vs 52% (15 of 29) for those receiving placebo ($P < .01$).

Conclusion The use of iNO was associated with a significantly reduced duration of mechanical ventilation and significantly greater rate of extracorporeal membrane oxygenation–free survival. *(J Pediatr 2015;166:365-9)*.

The acute respiratory distress syndrome (ARDS) results from severe inflammatory-mediated alveolar injury caused by pulmonary and extrapulmonary insults. Central to the pathophysiology of ARDS is the initiation of an inflammatory cascade that leads to sequestration, activation, and extravasation of neutrophils into the pulmonary interstitium and the release of tissue-destructive proteases. Diffuse capillary endothelial and alveolar epithelial damage ensue, leading to the development of interstitial and alveolar edema, the extravasation of plasma proteins, and the formation of alveolar hyaline membranes. Clinically, the syndrome is characterized by reduced lung compliance and volumes, intrapulmonary shunt and refractory arterial hypoxemia, and in most cases varying degrees of multiorgan system dysfunction.

In numerous trials investigators have evaluated strategies for improving oxygenation and improving outcomes in adults with ARDS. Low tidal volume ventilation has been shown to significantly improve survival in adult ARDS.[1] Despite this, the mortality rate in adult ARDS remains high, and other studies suggest that mortality has not decreased since the widespread adoption of the low tidal volume ventilation strategy.[2-5] And even though the mortality of ARDS is greater in adults than children, and despite the fact that outcomes in pediatric ARDS have improved during the last decade, the mortality in pediatric ARDS remains significant, ranging from 22% to 35%.[6-8]

Although inhaled nitric oxide (iNO) has been shown to significantly improve oxygenation in adults, the benefits are not sustained, and there is no beneficial impact on duration of ventilation or mortality.[9] Studies of iNO in children also have demonstrated a significant, albeit transient, improvement in oxygenation.[10,11] However, the impact of iNO on outcomes in pediatric ARDS has not been evaluated. The 2 prospective pediatric trials of iNO in children were either designed with or allowed for a crossover to iNO, precluding an assessment of impact on outcomes.[10,11]

We conducted a prospective, randomized placebo-controlled trial in children with ARDS to test the hypothesis that iNO would lead to improved oxygenation and shortened duration of mechanical ventilation. The primary outcome of the study was ventilator-free days at 28 days after randomization.

ARDS	Acute respiratory distress syndrome
CMV	Conventional mechanical ventilation
ECMO	Extracorporeal membrane oxygenation
FiO_2	Partial pressure of inspired oxygen
HFOV	High-frequency oscillatory ventilation
iNO	Inhaled nitric oxide
OI	Oxygenation index

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Methods

The study protocol was approved by the institutional review board at each participating center. Patient enrollment took place from 2003 through 2005. Because of slow enrollment, the study was terminated prematurely, and because of the acquisition of INO Therapeutics by Ikaria and a shift in clinical focus, the data were not analyzed until currently.

All patients meeting study criteria were eligible for the study and were approached for consent. Inclusion criteria consisted of the following: 44 weeks postconceptional age to 16 years of age; oxygenation index (OI) of ≥12 as determined by 2 separate measurements taken 30 minutes to 4 hours apart; chest radiograph with pulmonary infiltrates; mechanically ventilated ≤7 days; and signed institutional research board–approved informed consent. Exclusion criteria consisted of the following: immunocompromised host; history of bone marrow transplantation; active oncologic condition; received long-term (>30 days) or recent (<72 hours) high-dose glucocorticoids; right to left cardiac shunt; cardiovascular surgery within the last 14 days; status asthmaticus; treatment with iNO or other investigational medications within 24 hours before study initiation; chronically ventilated; and the decision by the primary care physician not to provide full support. Immunocompromised patients were excluded from the study because their mortality rate is exceptionally high and much greater than the mortality rate for patients with ARDS who are immunocompetent.

The centers involved and the number of patients enrolled (in parenthesis) at each were: Denver Children's Hospital (12), Denver, Colorado; Children's Healthcare of Atlanta (18), Atlanta, Georgia; Children's Hospital of Orange County (11), Orange, California; University of Chicago (3), Chicago, Illinois; Oregon Health and Science University (2), Portland, Oregon; University of Virginia Pediatric Critical Care (4), Charlottesville, Virginia; New York Presbyterian Hospital (2), New York, New York; Louisiana State University Health Sciences Center (2), Shreveport, Louisiana; and the Children's Hospital at Montefiore (1), Bronx, New York.

Patients were randomized by central registry. Study gas 5 ppm (nitric oxide or nitrogen) was administered continuously into the inspiratory limb of the ventilator circuit via a blinded version of the INOvent delivery system (Ikaria Corporation, Hampton, New Jersey). Gas initiation, and daily ventilator gas manipulation, was performed by a study therapist. The attending physician and care team were blinded to the study gas used and were not allowed to manipulate the blinded delivery system. Patients received study gas until death, until they were ventilator free, or at day 28 after enrollment, whichever came first. Daily spontaneous breathing trials were conducted once criteria were met. An extubated patient could resume study gas if they were reintubated within 24 hours and the patient study day was less than 28 days. If nitrogen dioxide levels exceeded 3 ppm or methemoglobin levels increased by >5% on 2 samples 6 hours apart, treatment gas was discontinued.

The guidelines for ventilatory management were established by the investigators in an attempt to minimize variation in practice. Patients receiving conventional mechanical ventilation (CMV) were managed via a low tidal volume strategy. Goal tidal volume was 4-8 mL/kg and a plateau pressure <30 cm H_2O. The end expiratory pressure was based on serial chest radiographs (every 6-12 hours) with a goal of expansion to 8 ribs posteriorly. Target arterial blood gas values were: pulse oximetry-derived arterial oxygen saturation 88%-95% with a partial pressure of inspired oxygen (FiO_2) <0.60, PaO_2 of 55-80 mmHg, and a pH of 7.25-7.40. High-frequency oscillatory ventilation (HFOV) settings were based on serial chest radiographs as described for CMV. Target FIO_2 and PaO_2 were the same as those for CMV. The FiO_2 was to be weaned over mean airway pressure until FiO_2 <0.60. According to the study protocol, patients were placed in the prone position for at least 8 hours daily. Patients receiving HFOV were transitioned to CMV before weaning. Weaning and extubation criteria were assessed daily. Daily spontaneous breathing trials were conducted when the following criteria were met: adequate spontaneous effort and positive end expiratory pressure ≤8 cm H_2O, FiO_2 ≤0.60, and SaO_2 ≥90%. Extubation criteria were met when the FiO_2 ≤0.60, pressure support ≤10 cmH_2O, and positive end expiratory pressure ≤6 cm H_2O. The study gas was discontinued 30 minutes before extubation, at which time the FiO_2 was increased by 0.15 over current value. The patient was considered successfully extubated if they remained so for greater than 24 hours.

Study measurements consisted of baseline pediatric risk of mortality scores (ie, Pediatric Risk of Mortality III), chest radiograph, arterial blood gas, determination of OI (mean airway pressure × FiO_2 × 100/PaO_2), methemoglobin level, and ventilatory settings. Subsequent arterial blood gases were obtained, and determinations of OIs were made at 4, 12, and 24 hours after initiation of study gas and at the time of extubation; methemoglobin levels were measured at 4 and 24 hours after initiation of study gas. Ventilator-free days at 28 days after randomization were determined for each patient. For subjects who died, days alive without mechanical ventilation were assigned a value of zero, and time on mechanical ventilation was calculated using the time of the first and last intubation. A patient was considered successfully extubated if they remained so for greater than 24 hours. Day zero was defined as the first 24 hours after initiation of study gas.

Statistical Analyses

Sample size determination was based on the following assumptions: the desired type 1 (alpha) error of 0.05 was the threshold for statistical significance (2-tailed); the difference in the number of days alive and free of mechanical ventilation to day 28 would be at least 3 days; the SD of the mean number of days alive and free of assisted breathing would be 9.8 days; and the desired power (1 − ß) for the trail was determined at 80%. Based on these assumptions, the minimum sample size for the trial was approximately 169 eligible patients per arm.