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Inhaled Nitric Oxide Use in Pediatric Hypoxemic Respiratory Failure

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Abstract

Objectives: To characterize contemporary use of inhaled nitric oxide (iNO) in pediatric acute respiratory failure and to assess relationships between clinical variables and outcomes. We sought to study the relationship of iNO response to patient characteristics including right ventricular (RV) dysfunction and clinician responsiveness to improved oxygenation. We hypothesize that prompt clinician responsiveness to minimize hyperoxia would be associated with improved outcomes.

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Design: An observational cohort study

Setting: Eight sites of the Collaborative Pediatric Critical Care Research Network

Patients: 151 patients who received iNO for a primary respiratory indication

Measurements: Clinical data were abstracted from the medical record beginning at iNO initiation and continuing until the earliest of 28 days, ICU discharge or death. Ventilator-free days, oxygenation index and Functional Status Scale were calculated. Echocardiographic reports were abstracted assessing for pulmonary hypertension, (RV) dysfunction, and other cardiovascular parameters. Clinician responsiveness to improved oxygenation was determined.

Main Results: One hundred thirty (86%) patients who received iNO had improved oxygenation by 24 hours. PICU mortality was 29.8%, while a new morbidity was identified in 19.8% of survivors. Among patients who had echocardiograms, 27.9% had evidence of pulmonary hypertension, 23.1% had RV systolic dysfunction and 22.1% had an atrial communication. Moderate or severe RV dysfunction was associated with higher mortality. Clinicians responded to an improvement in oxygenation by decreasing FiO_2 to < 0.6 within 24 hours in 71% of patients. Timely clinician responsiveness to improved oxygenation with iNO was associated with more ventilator-free days but not less cardiac arrests, mortality, or additional morbidity.

Conclusions: Clinician responsiveness to improved oxygenation was associated with less ventilator days. Algorithms to standardize ventilator management may improve signal to noise ratios in future trials enabling better assessment of the effect of iNO on patient outcomes. Additionally, confining studies to more selective patient populations such as those with RV dysfunction may be required.

Keywords

Pediatrics; Acute Respiratory Syndrome; Nitric Oxide; Pulmonary hypertension; Right ventricular failure; Morbidity

Background

Acute lung injury occurs in approximately 9% of mechanically ventilated children with 80% progressing to pediatric acute respiratory distress syndrome (PARDS) which is characterized by disruption of the alveolar capillary membrane resulting in the influx of protein-rich edema fluid into the alveoli. This process is associated with injury to the lung epithelium and vascular endothelium, dysregulated inflammation, uncontrolled activation of coagulation and loss of surfactant (1, 2). These pathophysiologic processes are clinically manifested as decreased lung compliance, ventilation perfusion mismatching, increased dead-space ventilation, intrapulmonary shunting and hypoxemia. Despite this understanding of the pathophysiology, the mainstay of acute respiratory distress syndrome (ARDS) therapy remains respiratory support with supplemental oxygen, positive end expiratory pressure (PEEP) and limited tidal volume mechanical ventilation as no adjunctive therapies have proven to be effective in PARDS.

Inhaled nitric oxide (iNO) has been suggested as a therapy for PARDS. It is well recognized as a potent and effective pulmonary vasodilator as it relaxes vascular smooth muscle by

increasing intracellular cyclic guanosine monophosphate. Its effects appear to be primarily local and short-lived as it is inactivated by hemoglobin once it diffuses across the alveolar capillary membrane into the bloodstream. Consequently, it would seem to be an ideal agent to ameliorate the ventilation perfusion mismatch of acute hypoxic respiratory failure thereby improving oxygenation, decreasing dead space ventilation and minimizing ventilator- and oxygen-induced lung injury (3). However, clinical trials to date have not been able to establish a clear benefit of its use.

Randomized control trials of iNO in pediatric and adult ARDS have demonstrated acute improvements in gas exchange, but iNO did not improve survival (4-10). Two recent meta-analyses of randomized control trials in adults failed to reveal a significant benefit of iNO on mortality (11,12). A meta-analysis of three pediatric trials with a total of only 162 patients failed to demonstrate either benefit or harm from iNO. (12). However, a pediatric study conducted between 2003 and 2005 but not included in the meta-analysis and which enrolled 55 patients demonstrated a higher rate of extracorporeal membrane oxygenation (ECMO) free survival in patients randomized to iNO as compared to placebo (13).

Current guidelines recommend targeting SpO_2 between 88-92% in more severe PARDS but only with scant pediatric data (14). Further, there is evidence that clinicians are slow to titrate oxygen in face of hyperoxia in children and adults (15, 16). Exposure to unnecessarily high FiO_2 levels may exacerbate acute lung injury and negate the beneficial effects of iNO. Hyperoxia alters a number of cellular pathways through the formation of reactive oxygen species, activation of apoptotic pathways and expression of inflammatory cytokines among others causing lung injury (17). A safe FiO_2 and duration of exposure has not been well established in humans, but in mechanically ventilated adults, exposure to excessively high FiO2 has been associated with mortality and longer durations of mechanical ventilation in some (18, 19) but not all studies (20). In an observational study, higher FiO2 was associated with mortality even after adjusting for physiologic score, admission type and PaO2/FiO2 ratio (19). Additionally, excessive oxygen exposure has been associated with worsened outcomes after cardiac arrest (21). Dissecting the effects of mechanical ventilation and oxygenation remain an area where additional study is needed.

Despite the predominance of negative studies, iNO continues be used in 12-13% of PARDS cases (22,23). Moreover, the recently convened Pediatric Acute Lung Injury Consensus Conference (PALICC) recommended that further study is needed to better define the role, if any, of iNO in the treatment of PARDS (3). Important questions remain in the use of iNO as it relates to ventilation strategies, patient positioning and use of echocardiography. Consequently, we assessed the use of iNO among the eight sites of the Collaborative Pediatric Critical Care Research Network (CPCCRN). We hypothesized that the potential benefit from iNO would be most manifested in those patients in whom the clinicians promptly responded to improvements in oxygenation to minimize potentially toxic respiratory support in a timely manner. In addition, we sought to characterize the contemporary use of iNO in PARDS and to assess the relationship between clinically relevant variables including clinician responsiveness and outcomes to better inform future clinical trial design.

Methods

Consecutive eligible patients treated with iNO for a primary respiratory indication in the pediatric or cardiac intensive care unit (ICU) of the eight CPCCRN institutions between October 15, 2015 and October 31, 2016 were included in this study. Eligible patients were less than 18 years of age and mechanically ventilated either before or within 24 hours of iNO. Newborns with congenital diaphragmatic hernia, meconium aspiration syndrome or persistent pulmonary hypertension of the newborn were excluded as were patients with iNO started at an outside institution or who were previously enrolled in the study. Patients with chronic pulmonary hypertension or who were intubated more than 24 hours after iNO initiation were excluded from analyses (n=11). The project was approved with waiver of informed consent by the responsible Institutional Review Board for every clinical site and the Data Coordinating Center at the University of Utah. Inhaled nitric oxide use in PARDS is not a U.S. Food and Drug Administration approved use and is considered off-label.

As this was an observational study, iNO administration and ventilator management was at the discretion of the treating physicians. All data were abstracted from the medical record. Data collection began at the time of iNO initiation and continued daily until 28 days, discharge from the ICU or death, whichever occurred first. Admission data included demographics, acute and chronic diagnoses, and pre-hospitalization technology dependence. Daily data collection included the use of ICU technologies (e.g. ECMO, hemodialysis/ hemofiltration), cardiac arrests, echocardiogram use, pulmonary hypertension medications and mechanical ventilation. Immediately prior to iNO initiation and for the next 48 hours, all changes of mechanical ventilator settings, blood gas measurements, and iNO dose changes as well as hourly pulse oximetry and end-tidal CO_2 values were collected. Functional Status Scale (FSS) was determined prior to ICU admission and at ICU discharge or 28 days (15). New ICU morbidity was defined as an increase in the FSS score of three or more.

The oxygenation index was calculated as the mean airway pressure (MAP) * FiO_2*100 / PaO_2, and the oxygen saturation index was calculated as MAP*FiO_2*100/SpO_2 for patients with $SpO_2 \leq 97\%$ where FiO_2 signifies the fraction of inspired oxygen, PaO_2 is the arterial partial pressure of oxygen, and SpO_2 is the pulse oximetry oxygen saturation(16). Ventilator-free days (VFDs) in the first 28 days were calculated from the intubation/ extubation logs starting on Day 0. Patients who died or required ventilation for more than 28 days were given 0 VFDs. In chronically ventilated patients, VFDs were calculated from the time of ICU admission to returning to baseline (pre-hospital) ventilator settings. Patients discharged from the hospital were assumed to be alive and not mechanically ventilated for the purpose of calculating 28-day mortality and VFDs. ICU and hospital lengths of stay were truncated for the five patients remaining in the ICU or in the hospital at study end. In each case, the duration was truncated at no less than eight months. Echocardiographic reports were abstracted to assess the presence of pulmonary hypertension, right ventricle (RV) dysfunction, tricuspid valve regurgitation, the presence of an atrial shunt, and congenital heart disease. The presence of pulmonary hypertension was defined as a tricuspid valve velocity > 3 meters/second, septal flattening during systole, or as a stated diagnosis in the report. Echocardiograms were obtained at the discretion of the treating physicians.

Graphs plotting ventilator settings, blood gas measurements and oxygenation were constructed. Clinician responsiveness was assessed in patients who sustained or achieved adequate oxygenation defined as either a SpO_2 greater than 88% or a PaO_2 greater than 60 mmHg within 24 hours of iNO initiation. We also assessed oxygenation improvement defined as a 20% decrease in OI or OSI within 24 hours of iNO initiation. Clinician responsiveness was defined as 'timely' if the FiO_2 was reduced to less than or equal to 0.6 by 24 hours, delayed if greater than 24 hours, or as no response if FiO_2 was never reduced to 0.6 or less.

Statistical Analysis:

Counts and percentages are reported for categorical variables while the median and interquartile ranges (IQR) are reported for continuous variables. Associations of ventilation and gas exchange variables with Day 28 mortality and with oxygenation improvement were assessed with the Wilcoxon rank-sum test. Modes of ventilation (Conventional vs. high frequency oscillatory ventilation [HFOV]) were compared using Fisher's exact test. In general, Fisher's exact test was used to assess associations for categorical variables while the Wilcoxon rank-sum test was used for continuous variables. Exceptions are footnoted when a more appropriate test was identified. Some of these exceptions include using the two-sided Cochran-Armitage test for trend to assess associations between tricuspid valve regurgitation and RV dysfunction variables with the binary outcomes oxygenation improvement and Day 28 mortality. Due to the sequential nature in the severity of the levels for both these variables, the Jonckheere-Terpstra test was used to assess their association with VFDs instead of the Kruskal-Wallis test (KW). For variables with more than two independent levels, such as atrial shunt present on study and primary respiratory dysfunction, associations with VFDs were assessed with KW. Analyses were performed using SAS 9.4 (SAS Institute; Cary, NC).

Results

During the study period, 151 patients with a respiratory indication for iNO were identified. Patient characteristics are summarized in Table 1. Slightly more than half of the patients were male. One hundred twelve patients (74.2%) had at least one chronic diagnosis prior to hospitalization. The most common chronic diagnoses were chromosomal abnormality (n=29), and cancer (n=22). Thirty-three patients (21.9%) were less than 37 weeks gestation at birth. Seven patients (4.6%) had a tracheostomy prior to hospitalization and five (3.3%) were chronically ventilated. Twenty-two patients (14.6%) were receiving oxygen,

Inhaled nitric oxide initiation occurred almost exclusively in the ICU (140 in the PICU and 10 in CICU). The median time from hospital admission to iNO initiation was 72.4 hours (IQR, 27.4, 181.1). Ten patients (6.6%) received iNO prior to intubation. The median time from the start of mechanical ventilation to iNO initiation was 30 hours (IQR, 5.8, 88.7) in the patients who had mechanical ventilation before iNO. The median duration of iNO use was 4 days (IQR, 2; 7). The recorded primary indication for iNO initiation was acute hypoxemic respiratory failure without elevated pulmonary artery pressure in 141 patients, elevated PA pressure in 5 and other or unknown in 5.

Mechanical ventilation parameters at iNO initiation for survivors versus non-survivors are listed in Table 2. Only median mean airway pressure (MAP) showed a significant difference and was higher among non-survivors. The median tidal volumes were 7.5 (IQR, 6.6; 8.9) and 7.9 (IQR, 6.5; 9.4) mL/kg in the two groups, respectively. The initial oxygenation and oxygen saturation indices were not significantly different between non-survivors and survivors.

One hundred thirty (86%) patients achieved or sustained an oxygen saturation > 88% or PaO2 > 60 mmHg by 24 hours (Table 3). Oxygenation responsivity was not different between patients on conventional versus HFOV. Patients who demonstrated improved oxygenation after starting iNO exhibited significantly higher PaO2 when measured, higher oxygen saturation or higher MAP at iNO initiation. One hundred patients were receiving iNO at 48 hours after initiation while 8 patients had died and 43 were no longer receiving iNO.

The use of advanced ICU therapies was high in this cohort with 23 patients (15.2%) receiving ECMO and 22 (14.6%) receiving continuous renal replacement therapy after Day 0 (Table 4). Forty-six patients (29.8%) died in the ICU. Two patients died after ICU discharge resulting in a hospital mortality of 31.1%. Patients who responded to iNO had significantly lower mortality compared to non-responders. Among PICU survivors, 21/106 patients (19.8%) had new morbidity defined as an increase in FSS score by three or more. The development of new morbidity did not differ between responders and non-responders. The median ICU length of stay in survivors responding to iNO was 21.50 days (IQR; 13.0, 36.0) compared to 13.52 days for non-survivors (IQR 7.5, 35.0).

Clinician responsiveness was assessed using plots of ventilator and patient monitoring (Supplemental Figures 1 & 2). Clinicians responded to an improvement in oxygenation by decreasing FiO_2 to < 0.6 within 24 hours in 92 patients (70.8%) (Table 5). Timely clinician responsiveness was associated with shorter duration of ventilation with a median of 13 days versus 18 days (p = 0.021). Likewise, timely responsiveness was associated with greater median VFDs (11 versus 4 days, p =0.022). Mortality at 28 days was similar between the 2 groups (22.8% versus 22.2%). The timing of hospital death as measured in calendar days from iNO initiation was not significantly associated with timely clinician responsiveness (p=0.1033). Twelve patients (9%) had a cardiac arrest after the initiation of iNO, but the rate did differ between groups. A new morbidity was seen in 17% of survivors and the rate did not differ by clinician response.

We also evaluated oxygenation improvement using change in OI and OSI. Thirty-five (23.2%) patients did not have the necessary data to calculate the OI or OSI at the time of iNO initiation. Thirteen had neither a PaO_2 from which to calculate an OI nor a SpO_2 value < 97% from which to calculate an OSI. Of the patients who had OI or OSI data available, 96 (82.8%) displayed oxygenation improvement as defined by a 20% decrease in OI or OSI by 24 hours after iNO initiation. Responders had a higher MAP, PEEP, and OI or OSI as compared to non-responders (Supplemental Table 1). There were no differences in outcomes related to oxygenation improvement after iNO treatment (Supplemental Table 2). Clinicians responded to oxygenation improvement by decreasing FiO_2 to 0.6 or less by 24 hours in

68/94 (72.3%) patients. (Supplemental Table 3) Clinician responsiveness was associated with more VFDs when compared to patients for whom the clinician had a delayed response or did not decrease the FiO_2 to 0.6 or less.

One hundred four patients (68.9%) had echocardiograms performed during the study period with 69 patients (45.7%) having an echocardiogram in the 12 hours before iNO initiation or on study Day 0 (Table 6). Twenty-nine patients (27.9%) had evidence of pulmonary hypertension documented with 17 patients' echocardiograms detecting pulmonary hypertension at or before iNO initiation. Mild right ventricular systolic dysfunction was observed in 16 patients (15.4%) and eight (7.7%) had moderate or severe dysfunction. Twenty-three (22.1%) patients had an atrial communication.

Patient characteristics (immunosuppression, diagnostic category) were not associated with a response to iNO, but were associated with mortality risk (Table 7 and supplemental table 4). Mortality was 72% among immunosuppressed patients compared to 21% in immunocompetent patients ($p < 0.001$). Diagnostic category and immunosuppression were associated with VFDs. The presence or absence of pulmonary hypertension as determined by echocardiography was not associated with oxygenation response to iNO, 28-day mortality, or VFDs. The presence of RV dysfunction was associated with higher mortality ($p=0.017$), despite the fact that a preponderance of these patients exhibited oxygen responsiveness to iNO.

Discussion

This study is one of the largest multicenter evaluations of the use of iNO for children with acute respiratory failure. In this project, clinician responsiveness to improved oxygenation with iNO by decreasing FiO_2 to < 0.6 was associated with more VFDs, but not mortality or less discharge morbidity in pediatric respiratory failure. One hundred thirty (85%) patients who received iNO had improved oxygenation by 24 hours. The only ventilator parameter that differed between those with and those without oxygenation improvement at iNO initiation was a higher MAP. Moreover, the observed mortality in this study was substantial (29.8% of patients died prior to PICU discharge), but consistent with two recent pediatric iNO studies that employed current "lung protective" ventilation practices (26, 27). Further, similar to the published literature, this study demonstrated that an immunocompromised condition was associated with higher mortality (28-30). Additionally, a new morbidity was identified in an additional 21 surviving patients (19.8%). Finally, among the subset of patients who had echocardiograms reported, 24.6% had evidence of pulmonary hypertension, 27.5% were noted to have RV systolic dysfunction and 20.3% had an atrial communication. The presence of moderate or severe RV dysfunction, but not pulmonary hypertension was associated with higher mortality.

The association of clinician responsiveness to improvements in oxygenation on outcomes is a central finding of this study. As reflected by the high overall mortality and the oxygenation index at the time of INO initiation, the use of iNO is apparently reserved for situations of severe lung disease requiring substantial and potentially toxic respiratory support. Presumably, the implementation of this therapy is to improve oxygenation, and thereby,

afford reduction in toxic ventilator support. The finding that patients whose treating clinicians reduced high levels of inspired oxygen had more VFDs suggests that such an approach may be beneficial as hyperoxia in acute lung injury has also been associated with longer duration of mechanical ventilation and lengths of stay (18-19). Moreover, these findings may improve the design of future studies of iNO use, which could be directed by adequately explicit algorithms to guide weaning ventilatory support if oxygenation improves. A comprehensive ventilator management algorithm seems essential to designing successful future trials. Such algorithms will need to include oxygenation goals, timeliness to reducing therapy, and titration of ventilation parameters including PEEP. Our finding along with others that responders to iNO had higher MAP at initiation suggests the important role of ventilator strategy in the use of ancillary treatments in PARDs (31). In our study, inspired oxygen was not reduced at all in 8% of the patients despite an improvement in oxygenation. This rate of apparent failure to act is not unique to this study. In a prospective, observational comparison of ventilator changes performed compared to recommendations from a modified ARDSNet protocol, pediatric intensivists failed to make recommended changes in 56% of the opportunities, and made changes opposite of the recommendations in 12% of the cases (14).

In addition to standardized ventilator interventions, the present data suggest other parameters that may be potentially important in designing a clinical trial of iNO for pediatric acute hypoxic respiratory failure. For example, mortality may not be an appropriate primary endpoint for such a trial. In this study, clinician responsiveness was not associated with improved survival, but was associated ventilator-free days. The lack of association with mortality may not be surprising as many of the risk factors for death in pediatric acute lung injury are not specific to the pulmonary system (29-31). The pivotal trials leading to US Food and Drug Administration approval for iNO in neonates demonstrated less ECMO use, but no difference in mortality (32, 33). Currently, some data exist supporting such a role for iNO in PARDS. In a randomized trial of iNO in PARDS, Bronicki et al found decreased ECMO use and increased ventilator-free days associated with iNO (13). Dowell et al also reported fewer ventilator days as well as reduced use of high-frequency oscillatory ventilation and ECMO among PARDS patients who responded to iNO therapy (27). In a recent propensity matched analysis, however, positive response to iNO was not associated with mortality or VFDs (10).

Additionally, while mortality is a challenging primary endpoint among an unselected, heterogeneous population of PARDS patients, there may be subgroups with substantial mortality risk that will benefit from iNO. An immunocompromised state clearly identifies a group of children at increased risk of dying from PARDS. Given the difference in mortality among the immunocompromised, any trial will at a minimum need to clearly define an immunocompromised child and stratify enrollment accordingly. However, identification of other appropriate subgroups may not be as straightforward. For instance, the degree of lung injury and required mechanical ventilator support may not adequately identify useful subgroups to study. In this study, neither mechanical ventilation settings nor oxygenation index distinguished survivors and non-survivors. Further, a recent meta-analysis failed to demonstrate a threshold of PaO_2/FiO_2 between 70 and 200 mmHg at which iNO treated patients had lower mortality relative to controls (11).

Assessing right ventricular function may represent an opportunity to identify a subgroup of patients in whom iNO and other targeted pulmonary hypertension therapies may be of particular benefit. In our study, 23% of the patients with an echocardiogram had evidence of RV dysfunction which was associated with an increased mortality risk. Acute cor pulmonale defined as acute right ventricle dilation, dysfunction or both has been reported in 40% of children and 22-50% of adults with ARDS (34, 35). While a direct causal relationship between acute cor pulmonale and mortality is not established, our study and several, but not all studies, have found a higher mortality rate in patients with significant RV dysfunction (34-40). The difference in association may be related to how RV dysfunction is detected and its severity. In a retrospective analysis of PARDS patients who had an echocardiogram within first 24 hours of diagnosis, RV dysfunction as defined by RV global longitudinal strain but no other measures were associated with mortality and lower probability of extubation (34). Evidence of pulmonary hypertension was not associated with mortality. In a prospective study of 752 adult ARDS patients, higher hospital mortality was only observed in those with severe RV dilation and not in those with RV dysfunction without dilation (41). Additionally, RV dysfunction may also be associated with increased length of mechanical ventilation (34, 39) increase use of prone positioning and iNO use (37,38). Future studies should address the role of routine echocardiography in identifying cardiac dysfunction in PARDS patients. The selection of which parameters to use in assessing RV function (e.g. fractional area change, tricuspid annular plane excursion, and strain analysis) is not standardized among institutions and hence requires prospective validation.

The precipitant of RV dysfunction observed in ARDS is multifactorial and associated in large part to elevated RV afterload secondary to hypoxic vasoconstriction, hypercapnia, acidemia, and an altered balance between vasoconstrictor and vasodilators (35). Further, pulmonary vascular resistance increases at the extremes of lung volumes. At low volumes, there is extra-alveolar vessel and airway collapse with hypoxic vasoconstriction. At high lung volumes, increased pulmonary vascular resistance occurs due to collapse of intra-alveolar vessels. Adults with higher plateau and /or positive end expiratory pressure (PEEP) appear to have higher levels of RV failure (42,43). Further research into whether altering pulmonary vascular tone with iNO or other agents in patients with ARDS associated RV dysfunction will improve patient outcomes is warranted.

The prevalence of an atrial communication in adults with ARDs has been reported to range between 15-19% (37, 44, 45). Intra-atrial shunting may worsen hypoxemia and may cofound assessment of the severity of lung disease when oxygen parameters are used. The presence of an atrial communication may limit the benefit of alveolar recruitment with PEEP. In adults with ARDS, an atrial communication was associated with smaller improvement in PaO2/FiO2 ratio during PEEP titration (44). Further, higher PEEP levels resulted in more patients developing a right to left atrial shunt. In contrast, an atrial communication may be beneficial in the presence of right ventricular failure by maintaining cardiac output and decompressing the right ventricle. Similar to adult studies, an atrial communication was associated with improved oxygenation but not VFDs or mortality.

In this observational study, the use of inhaled nitric oxide was at the discretion of the treating clinicians. Consequently, the variables that clinicians used in their decision making

are unknown and not based on a consensus protocol. Decisions about mechanical ventilation and iNO use may not have been based entirely on respiratory goals. As the primary purpose of the study was to assess clinician responsiveness, we utilized oxygenation parameters (SpO2 and PaO2) as our primary analysis rather than OI to mitigate the effects of ventilator management decisions on assessing patient response. In a sensitivity analysis, we analyzed oxygenation improvement based on OI or OSI parameters, and our findings were similar in regards to characteristics and outcomes of patients whose clinicians responded to improved oxygenation by decreasing FiO_2 in responders. Importantly, the analysis using OI or OSI had more missing data than the analysis done using SpO2 and PaO2 to define oxygenation improvement. A total of 35 patients did not have OI or OSI data. Due to the declining use of arterial lines, only 67% of patients had blood gas data available at iNO initiation to calculate an OI. Thirteen of the 35 patients did not have a PaO_2 measured and had a $SpO_2 > 97\%$ at the time of iNO initiation, thus, making OSI an inappropriate alternative.

Although the PALICC guidelines do not recommend the use of iNO for routine PARDS, they do suggest that it may be considered for severe RV dysfunction. Additionally, the PALICC consensus statement includes the need for further studies to better define the role of iNO for PARDS (3). Although the current study is limited by its lack of a control group and the absence of any proscribed guidelines for the use of iNO, it does provide multicenter data from a large cohort of pediatric patients with acute respiratory failure that may be useful in designing a future randomized trial. First, it would seem clear that a standard approach to ventilation with strict adherence to predefined guidelines for ventilator management prior to and after iNO initiation is essential. In this study, the prompt response to improvements in oxygenation was associated with a shorter duration of mechanical ventilation. Second, it identifies potential outcome parameters with true clinical significance that may be used to power an iNO trial. Although it may be challenging to achieve an adequate power to test for an effect on mortality, iNO may impact other clinically meaningful outcomes such as VFDs and frequency of cardiac arrests. Third, it identifies high risk subgroups of patients that may help assess a role for iNO. For example, any trial of iNO will need to account for the presence of an immunocompromised state and balance enrollment between treatment arms. Additionally, children with RV dysfunction as a component of their acute respiratory failure may represent a subgroup most likely to benefit from this therapy.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1.

Demographics of inhaled nitric oxide use

	Overall (N = 151)
Male	83 (55.0%)
Age [1]	
Neonate < 1 month	5 (3.3%)
Infant < 1 year	47 (31.1%)
Child < 12 years	82 (54.3%)
Adolescent 12 to 18 years	17 (11.3%)
Race	
White	81 (53.6%)
Black or African American	45 (29.8%)
Other and Unknown	25 (16.6%)
Ethnicity	
Hispanic or Latino	19 (12.6%)
Not Hispanic or Latino	128 (84.8%)
Unknown or Not Reported	4 (2.6%)
Any chronic diagnosis [2]	112 (74.2%)
Chromosomal defect	29 (19.2%)
Cancer	22 (14.6%)
Lung disease of infancy (BPD)	14 (9.3%)
Bone transplant	8 (5.3%)
Organ transplant	1 (0.7%)
Pre-hospital technology dependence	39 (25.8%)
Echo obtained within the 12 hours prior to iNO initiation	33 (21.9%)
At least one echo obtained on study	105 (69.5%)
Cardiac catheterization prior to iNO	2 (1.3%)

[1]Definition of age categories:

Neonate: < 1 month

Infant: < 1 year

Child: < 12 years

Adolescent: 12 years to 18 years

[2]Only select chronic diagnoses are listed. Subjects may have multiple chronic diagnoses.

Table 2.

Ventilation and gas exchange at inhaled nitric oxide initiation with Day 28 mortality

	Day 28 mortality		
	Dead (N = 45) [Q1, Median, Q3]	**Alive (N = 106) [Q1, Median, Q3]**	**P-value**
Ventilation type[1,2]			0.372[2]
Conventional	37/133 (27.8%)	96/133 (72.2%)	
HFOV	6/15 (40.0%)	9/15 (60.0%)	
NA	2/3 (66.7%)	1/3 (33.3%)	
PaO2 (mmHg)	n=34 [55.0, 67.0, 82.0]	n=71 [54.1, 64.0, 78.3]	0.742[3]
SpO_2 (%)	n=42 [89.0, 92.5, 96.0]	n=103 [90.0, 94.0, 97.0]	0.297[3]
Exhaled tidal volume (mL/kg)	n=25 [6.6, 7.5, 8.9]	n=75 [6.5, 7.9, 9.4]	0.535[3]
MAP (cmH_2O)	n=35 [16.0, 21.0, 30.1]	n=91 [14.0, 18.0, 22.0]	0.035[3]
FiO_2	n=44 [0.7, 0.9, 1.0]	n=106 [0.7, 0.9, 1.0]	0.743[3]
PEEP (cmH_2O)	n=37 [6.0, 12.0, 14.0]	n=95 [8.0, 10.0, 12.0]	0.352[3]
PIP (cmH_2O)	n=34 [31.0, 33.0, 38.0]	n=91 [27.0, 32.0, 36.0]	0.113[3]
$ETCO_2$ (mmHg)	n=27 [27.0, 35.0, 48.0]	n=64 [31.5, 41.0, 54.0]	0.099[3]
Oxygenation index	n=26 [16.1, 24.0, 39.1]	n=60 [13.9, 20.8, 31.8]	0.489[3]
Oxygenation saturation index	n=28 [12.8, 19.3, 25.0]	n=70 [12.7, 16.6, 22.0]	0.269[3]
Time between iNO initiation and mechanical ventilation initiation (hours)	n=41 [5.5, 45.2, 128.2]	n=100 [6.7, 29.9, 82.7]	0.325[3]

[*] If a parameter value was not entered at inhaled nitric oxide initiation, the closest prior value to initiation was used. Ventilation parameters up to 6 hours prior to iNO initiation were considered.

[1] Row percentages are reported.

[2] Fisher's exact test was used to compare mortality between conventional and HFOV ventilation modes. 1 subject was started on mechanical ventilation after iNO initiation and 2 subjects did not have ventilation type recorded at time of iNO initiation. Reported as NA.

[3] Wilcoxon rank-sum test.

Table 3.

Ventilation and gas exchange at inhaled nitric oxide initiation based on oxygenation improvement *

	Oxygenation improvement			
	No (N = 11) [Q1, Median, Q3]	**Yes (N = 130) [Q1, Median, Q3]**	**Unable to determine (N = 10)**	**P-value**
Ventilation type [1,2]				0.598 [2]
Conventional	10/133 (7.5%)	116/133 (87.2%)	7/133 (5.3%)	
HFOV	0/15 (0.0%)	13/15 (86.7%)	2/15 (13.3%)	
NA	1/3 (33.3%)	1/3 (33.3%)	1/3 (33.3%)	
PaO2 (mmHg)	n=8 [39.4, 44.7, 59.5]	n=89 [56.4, 67.0, 80.7]	n=8 [53.5, 62.6, 78.0]	0.018 [3]
SpO_2 (%)	n=10 [69.0, 79.5, 91.0]	n=127 [90.0, 93.0, 97.0]	n=8 [91.5, 93.5, 96.5]	<.001 [3]
Exhaled tidal volume (mL/kg)	n=7 [6.6, 8.0, 9.6]	n=86 [6.5, 7.9, 9.3]	n=7 [5.0, 7.4, 7.9]	0.844 [3]
MAP (cmH_2O)	n=7 [10.0, 13.0, 15.0]	n=110 [15.0, 19.0, 24.0]	n=9 [16.0, 16.0, 25.0]	0.002 [3]
FiO_2	n=11 [0.9, 1.0, 1.0]	n=130 [0.7, 0.9, 1.0]	n=9 [0.6, 0.6, 0.8]	0.318 [3]
PEEP (cmH_2O)	n=10 [5.0, 8.5, 15.0]	n=115 [8.0, 10.0, 12.0]	n=7 [6.0, 10.0, 10.0]	0.392 [3]
PIP (cmH_2O)	n=9 [27.0, 30.0, 32.0]	n=109 [27.0, 32.0, 36.0]	n=7 [30.0, 32.0, 38.0]	0.455 [3]
$ETCO_2$ (mmHg)	n=8 [19.5, 28.5, 42.0]	n=77 [30.0, 38.0, 52.0]	n=6 [43.0, 50.0, 61.0]	0.090 [3]
Oxygenation index	n=5 [19.3, 21.6, 37.1]	n=74 [13.0, 22.7, 36.1]	n=7 [16.1, 16.6, 19.5]	0.880 [3]
Oxygenation saturation index	n=7 [12.3, 15.9, 19.6]	n=83 [13.2, 18.1, 23.5]	n=8 [9.1, 9.9, 20.6]	0.362 [3]
Time between iNO initiation and mechanical ventilation initiation (hours)	n=11 [4.4, 22.2, 45.0]	n=121 [6.2, 30.0, 92.5]	n=9 [32.3, 64.7, 152.5]	0.313 [3]

* Oxygenation improvement defined as either an SpO_2 greater than 88% or a PaO_2 greater than 60 mmHg within 24 hours of iNO initiation. If a parameter value was not entered at inhaled nitric oxide initiation, the closest prior value to initiation was used. Ventilation parameters up to 6 hours prior to iNO initiation were considered.

[1] Row percentages are reported.

[2] Fisher's exact test was used to compare mortality between conventional and HFOV ventilation modes. 1 subject was started on mechanical ventilation after iNO initiation and 2 subjects did not have ventilation type recorded at time of iNO initiation. Reported as NA.

[3] Wilcoxon rank-sum test.

Table 4.

Outcomes

	Oxygenation improvement on iNO*			
	No (N = 11)	**Yes (N = 130)**	**Unable to determine (N = 10)**	**P-value**
ECMO after Day 0	4 (36.4%)	18 (13.8%)	1 (10.0%)	0.070[5]
Cardiac arrest after Day 0	4 (36.4%)	13 (10.0%)	1 (10.0%)	0.029[5]
CVVH/dialysis after Day 0	2 (18.2%)	19 (14.6%)	1 (10.0%)	0.669[5]
Days on continuous iNO	1.0 [0.0, 7.0]	4.0 [2.0, 7.0]	0.5 [0.0, 1.0]	0.049[6]
Intensive care unit (ICU)				
Mortality	8 (72.7%)	32 (24.6%)	5 (50.0%)	0.002[5]
New morbidity (among survivors)	1 (33.3%)	20 (20.4%)	0 (0.0%)	0.507[5]
Length of stay (days)				
Overall	7.0 [2.0, 59.0]	20.0 [11.0, 36.0]	14.5 [12.0, 34.0]	0.034[6]
Survivors[1]	59.0 [3.0, 65.0]	21.5 [13.0, 36.0]	13.0 [13.0, 16.0]	0.542[6]
Non-Survivors[1]	5.0 [1.5, 11.0]	13.5 [7.5, 35.0]	28.0 [7.0, 34.0]	0.046[6]
Day 28				
Mortality[2]	8 (72.7%)	31 (23.8%)	6 (60.0%)	0.002[5]
Ventilator-free days[3]	0.0 [0.0, 0.0]	7.5 [0.0, 17.0]	4.0 [0.0, 18.0]	0.017[6]
Hospital				
Mortality	8 (72.7%)	33 (25.4%)	6 (60.0%)	0.002[5]
Length of stay (days)				
Overall	8.0 [2.0, 75.0]	30.0 [18.0, 56.0]	32.0 [19.0, 43.0]	0.024[6]
Survivors[4]	75.0 [8.0, 88.0]	31.0 [22.0, 55.0]	24.0 [21.0, 61.0]	0.628[6]
Non-survivors[4]	5.0 [1.5, 14.0]	21.0 [8.0, 61.0]	39.5 [7.0, 43.0]	0.037[6]

*Oxygenation improvement defined as either an SpO_2 greater than 88% or a PaO_2 greater than 60 mmHg within 24 hours of inhaled nitric oxide initiation.

[1]Survivors for ICU length of stay included all subjects discharged from the ICU alive.

[2]Day 28 mortality was assessed at Day 28 or hospital discharge, whichever came first.

[3]If the subject died within twenty-seven calendar days post iNO initiation (on Day 27 or before) or the subject required mechanical ventilation for 28 Days or more, then the ventilator-free days (VFD) = 0. If the subject was successfully weaned from mechanical ventilation within 28 Days, VFDs equaled 28 minus the number of days on mechanical ventilation. For chronically ventilated subjects, the VFDs equaled 28 minus the number of calendar days from mechanical ventilation initiation to returning to baseline or stable ventilator settings. Â If these subjects did not return to baseline before 28 Days, then the VFDs = 0.

[4]Survivors for hospital length of stay included all subjects discharged from the hospital alive.

*Five subjects were still in the hospital at study end. Two of the five were still in the ICU. Hospital and ICU length of stay for these subjects are truncated between 8-15 months and 8-10 months respectively.

[5] Fisher's exact test.

[6] Wilcoxon rank-sum test.

Table 5.

Outcomes associated with clinician response to oxygenation improvement*

	Clinician response			
	None or delayed (N = 36)	Timely (N = 92)	Unable to determine (N = 2)	P-value
ECMO after Day 0	2 (5.6%)	16 (17.4%)	0 (0%)	0.097[3]
Days on mechanical ventilation	18.0 [12.0, 31.0]	13.0 [9.0, 21.0]	2.5 [2.0, 3.0]	0.021[4]
Ventilator-free days	4.0 [0.0, 13.0]	11.0 [0.0, 18.0]	0.0 [0.0, 0.0]	0.022[4]
Cardiac arrest on Day 0	2 (5.6%)	8 (8.7%)	1 (50.0%)	0.724[3]
Cardiac arrest after Day 0	4 (11.1%)	8 (8.7%)	1 (50.0%)	0.739[3]
CVVH/dialysis after Day 0	7 (19.4%)	12 (13.0%)	0 (0%)	0.410[3]
ICU length of stay (days)[1]	23.0 [12.0, 45.0]	20.0 [12.0, 36.0]	1.5 [1.0, 2.0]	0.618[4]
Hospital length of stay (days)[1]	28.5 [17.5, 52.5]	30.5 [19.5, 58.5]	1.5 [1.0, 2.0]	0.441[4]
Day 28 mortality				1.000[3]
Dead	8 (22.2%)	21 (22.8%)	2 (100.0%)	
Alive	28 (77.8%)	71 (77.2%)	0 (0%)	
Survivors				
Total	28	71	0	
New morbidity[2]				0.108[3]
No	19 (67.9%)	59 (83.1%)	0 (0%)	
Yes	9 (32.1%)	12 (16.9%)	0 (0%)	

*Table includes subjects whose oxygenation improved on iNO. Oxygenation improvement defined as either an SpO_2 greater than 88% or a PaO_2 greater than 60 mmHg within 24 hours of iNO initiation.

[1]Five subjects were still in the hospital at study end. Two of the five were still in the ICU. Hospital and ICU length of stay for these subjects were truncated between 8-15 months and 8-10 months respectively.

[2]A new morbidity was defined as an increase (worsening) in the Functional Status Scale (FSS) by three or more from baseline to ICU discharge or Day 28.

[3]Fisher's exact test.

[4]Wilcoxon rank-sum test.

ECMO - Extracorporeal membrane oxygenation

CVVH - Continuous veno-venous hemofiltration

ICU - Intensive care unit

Table 6.

Echocardiogram report abstractions

	Initiation[1] (N = 69)	On Study[2] (N = 104)
Pulmonary hypertension present	17 (24.6%)	29 (27.9%)
Tricuspid valve regurgitation		
Severe	1 (1.4%)	2 (1.9%)
Moderate	10 (14.5%)	12 (11.5%)
Mild	10 (14.5%)	14 (13.5%)
Trivial	37 (53.6%)	66 (63.5%)
None	11 (15.9%)	10 (9.6%)
RV dysfunction		
Severe	2 (2.9%)	2 (1.9%)
Moderate	6 (8.7%)	6 (5.8%)
Mild	11 (15.9%)	16 (15.4%)
Normal	50 (72.5%)	80 (76.9%)
Atrial shunt present		
Right-to-left	4 (5.8%)	5 (4.8%)
Bi-directional	1 (1.4%)	6 (5.8%)
Left-to-right	9 (13.0%)	12 (11.5%)
None	55 (79.7%)	81 (77.9%)

[1]The initiation window is defined as the 12 hours prior to inhaled nitric oxide initiation or on the calendar day inhaled nitric oxide was begun. Subjects without echocardiogram abstractions during this window are excluded from this column.

[2]On Study refers to during the initiation window or Day 0 - through Day 28 or intensive care unit discharge, whichever occurred first. Subjects without any echocardiogram abstractions are excluded from this table.

[*]Subjects with 'Not reported' conditions are classified as 'None' or 'Normal'.

Table 7.

Outcomes associated with pre-inhaled nitric oxide parameters and echocardiogram report abstractions

	Oxygenation Improvement*		Day 28 Mortality		Ventilator-Free Days	
	Yes (N = 130)	P-Value	Dead (N = 45)	P-Value	VFD	P-Value
PRE-EXISTING CONDITIONS						
Premature (< 37 weeks gestation)		0.121[1]		0.133[1]		0.243[2]
No	99/110 (90%)		38/117 (32%)		4.0 [0.0, 17.0]	
Yes	30/30 (100%)		6/33 (18%)		11.0 [1.0, 18.0]	
Unknown	1/1 (100%)		1/1 (100%)		0.0 [0.0, 0.0]	
Immunosuppression		1.000[1]		<.001[1]		0.028[2]
No	109/119 (92%)		27/126 (21%)		8.0 [0.0, 17.0]	
Yes	21/22 (95%)		18/25 (72%)		0.0 [0.0, 15.0]	
Primary respiratory dysfunction		0.535[1]		0.005[1]		0.028[4]
ALI/ARDS non pulmonary etiology	29/35 (83%)		14/37 (38%)		11.0 [0.0, 19.0]	
ALI-sepsis	35/37 (95%)		20/40 (50%)		0.0 [0.0, 5.0]	
Asthma	2/2 (100%)		0/2 (0%)		15.0 [15.0, 15.0]	
Lower Respiratory Tract Disease - aspiration	10/10 (100%)		3/10 (30%)		8.5 [0.0, 14.0]	
Lower Respiratory Tract Disease - bacterial	10/10 (100%)		2/11 (18%)		4.0 [0.0, 14.0]	
Lower Respiratory Tract Disease - viral (not RSV)	29/31 (94%)		4/35 (11%)		13.0 [5.0, 18.0]	
Lower Respiratory Tract Disease - RSV	13/14 (93%)		2/14 (14%)		5.0 [0.5, 15.5]	
Other or unknown	2/2 (100%)		0/0 (0%)		24.0 [24.0, 24.0]	
ECHO ABSTRACTIONS ON STUDY[6]						
Pulmonary Hypertension present on study		0.106[1]		0.350[1]		0.355[2]
No	65/73 (89%)		21/75 (28%)		4.5 [0.0, 16.0]	
Yes	26/26 (100%)		11/29 (38%)		0.5 [0.0, 11.0]	
Tricuspid valve regurgitation on study		0.498[3]		0.037[3]		0.117[5]
Severe	2/2 (100%)		2/2 (100%)		0.0 [0.0, 0.0]	
Moderate	9/11 (82%)		7/12 (58%)		0.0 [0.0, 0.0]	
Mild	13/13 (100%)		3/14 (21%)		8.0 [0.0, 17.0]	

	Oxygenation Improvement*		Day 28 Mortality		Ventilator-Free Days	
	Yes (N = 130)	P-Value	Dead (N = 45)	P-Value	VFD	P-Value
Trivial	61/64 (95%)		16/66 (24%)		4.5 [0.0, 16.0]	
None	6/9 (67%)		4/10 (40%)		4.5 [0.0, 15.0]	
RV dysfunction on study		0.367[3]		0.017[3]		0.191[5]
Severe	2/2 (100%)		1/2 (50%)		0.0 [0.0, 0.0]	
Moderate	6/6 (100%)		5/6 (83%)		0.0 [0.0, 0.0]	
Mild	14/15 (93%)		5/16 (31%)		5.0 [0.0, 19.0]	
Normal	69/76 (91%)		21/80 (26%)		4.5 [0.0, 16.0]	
Atrial shunt present on study		0.034[1]		0.316[1]		0.135[4]
Right-to-left	4/5 (80%)		3/5 (60%)		0.0 [0.0, 0.0]	
Bi-directional	6/6 (100%)		2/6 (33%)		3.5 [0.0, 17.0]	
Left-to-right	7/10 (70%)		5/12 (42%)		5.5 [0.0, 12.0]	
None	74/78 (95%)		22/81 (27%)		5.0 [0.0, 16.0]	

Percentages reported are row percentages.

*Oxygenation improvement defined as either an SpO_2 greater than 88% or a PaO_2 greater than 60 mmHg within 24 hours of iNO initiation. If Oxygenation Improvement='Unable to determine' (N=10) and counts for subjects with 'No echo obtained'(30 percent of respiratory subjects) are excluded from this table and do not contribute to p-value calculations.

[1]Fisher's exact test.

[2]Wilcoxon rank-sum test.

[3]Cochran-Armitage trend test.

[4]Kruskal-Wallis test.

[5]Jonckheere-Terpstra test.

[6]Only subjects with at least on echocardiogram report abstraction obtained on study are included.

ALI - Acute lung injury

ARDS - Acute respiratory distress syndrome

RSV - Respiratory syncytial virus

RV - Right ventricle