Clinical Indication for Use and Outcomes After Inhaled Nitric Oxide Therapy

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Background. **Inhaled nitric oxide (iNO) use is widespread, but the long-term outcomes after therapy in adult patients remain unknown.**

Methods. **All 376 patients receiving perioperative iNO (excluding pediatric and interventional cardiology procedures) at Columbia University Medical Center were prospectively followed from 2000 to 2003. Survival data were collected from chart review.**

Results. **Inhaled nitric oxide was used to treat pulmonary and right ventricular failure in patients undergoing orthotopic heart transplantation (OHT, n = 67), orthotopic lung transplantation (n = 45), cardiac surgery (n = 105), and ventricular assist device placement (n = 66), and for hypoxemia in other surgery (n = 34) and medical patients (n = 59). Average follow-up was 2.9 ± 1.0 years. Overall mortality was lowest when iNO was used after OHT (25.4%) and orthotopic lung transplantation (37.8%), intermediately after cardiac surgery (61%), ventricular assist device (62%), and other surgery patients (75%), and highest among medical patients (90%; all $p < 0.005$). The cost of iNO therapy was lower in transplantation versus medical patients, with a trend toward shorter duration of use. In multivariate analysis, respiratory failure and use in non-OHT were independent predictors of mortality (both $p = 0.001$). A risk score greater than 1 (score = non-OHT use 1, plus right ventricular failure 1) predicted a mortality of 76.5% versus 37.2% ($p < 0.001$).**

Conclusions. **Use of iNO for pulmonary hypertension in patients undergoing OHT and orthotopic lung transplantation was associated with a significantly lower overall mortality rate compared with its use after cardiac surgery or for hypoxemia in medical patients. Inhaled nitric oxide does not appear to be cost effective when treating hypoxemia in medical patients with high-risk scores and irreversible disease.**

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Despite limited data on its benefit on patient outcomes, inhaled nitric oxide (iNO) is an established pulmonary vasodilator in adult and pediatric critical care settings [1]. It selectively vasodilates pulmonary vessels through cyclic guanosine monophosphate production in pulmonary smooth muscle cells [2], and its adsorption by hemoglobin prevents the induction of systemic hypotension. Its ability to rapidly decrease pulmonary artery pressures (PAP) and pulmonary vascular resistance (PVR) and improve gas exchange has led to its use in primary pulmonary hypertension [3, 4], chronic obstructive pulmonary disease [5], adult respiratory distress syndrome (ARDS) [6], sickle cell anemia [7], and after orthotopic heart transplantation (OHT) and orthotopic lung transplantation (OLT) [8–10]. Inhaled nitric oxide is also the diagnostic agent of choice for assessing pulmonary vasculature response to oral vasodilators in patients with primary pulmonary hypertension [11]. It is utilized after OHT, OLT, and congenital and adult cardiac surgery for right ventricular (RV) afterload reduction [12–14], reduction of ischemia-reperfusion injury [10], and improvement of allograft function [8–10]. Pulmonary vasodilators that act through cyclic adenosine monophosphate, such as prostacyclin, produce similar effects on pulmonary vasculature, but also induce systemic vasodilatation [15].

Inhaled nitric oxide is approved by the Food and Drug Administration (FDA) for only one indication: persistent pulmonary hypertension of the newborn. Although iNO therapy has not been demonstrated to decrease overall mortality, it improves oxygenation in this population and decreases the duration of mechanical ventilation, as well as the need for extracorporeal membrane oxygenation [16–18]. In adults with ARDS, iNO improves oxygenation and ventilation-perfusion mismatch but does not improve survival at 30 days [19, 20]. In fact, use of iNO has not been shown to improve survival at any timepoint in any patient population [16, 17, 21, 22], while lengthy periods of iNO treatment substantially increase intensive care costs [23]. Studies addressing the long-term survival of specific adult populations who may benefit from iNO therapy, such as OHT or OLT patients, do not exist and may help guide more judicious and cost-effective use.

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Abbreviations and Acronyms

ARDS = adult respiratory distress syndrome
iNO = inhaled nitric oxide
OHT = orthotopic heart transplantation
OLT = orthotopic lung transplantation
PAP = pulmonary artery pressure
PVR = pulmonary vascular resistance
ROC = receiver operating curve
RV = right ventricular
VAD = ventricular assist device

The objective of the present study was to evaluate long-term outcomes and acquisition costs associated with iNO therapy in adult cardiopulmonary transplantation, cardiac surgery, ventricular assist device (VAD) implantation, other surgery, and medical subgroups.

Material and Methods

Study Design

Data on all patients receiving iNO at Columbia University Medical Center from 2000 to 2003 were prospectively collected and retrospectively analyzed for the purposes of this study. Pediatric patients (<18 years) and patients receiving short-term iNO for diagnostic purposes in the cardiac catheterization laboratory were excluded. Institutional guidelines for iNO administration are listed in Table 1. Additional off-guideline utilization of iNO was allowed for the treatment of life-threatening hypoxemia after acute respiratory decompensation, as a potentially life-saving therapy. Use in this immediate setting required departmental approval, and approval was granted on a case-by-case basis.

Clinical data were obtained from chart review. Patients were separated into surgical and nonsurgical groups, and further categorized by the primary surgical procedure performed: OHT, OLT, cardiac surgery (including adult congenital cardiac surgery), VAD implantation, and other surgery (including nonthoracic organ transplantation). A patient was classified as a surgical patient if iNO was administered within the hospital admission of surgery. Subjects not undergoing surgery were classified as medical patients. The study was approved and informed consent waived by the Institutional Review Board; all procedures were in accordance with institutional guidelines.

Table 1. Institutional Guidelines for Inhaled Nitric Oxide Administration

Heart transplantation with evidence of pulmonary hypertension
Complicated coronary surgery with evidence of right ventricular failure based on at least one of the following criteria
Mean pulmonary artery pressure $\geq$ 25 mm Hg
Echocardiographic evidence of moderate to severe right ventricular dysfunction; severe right atrial or ventricular enlargement
Cardiac index $\leq$ 2.2 L $\cdot$ min^{-1} $\cdot$ m^{-2}
Precapillary pulmonary hypertension diagnosis
Congenital cardiac disease
Acute chest syndrome in sickle cell disease

The starting dose for all above indications was 10 to 20 ppm, with an initial trial for 60 minutes before up-titration.

Table 2. Patient Clinical Variables

Demographics
Age
Sex
Comorbidities
Diabetes mellitus
Hypertension
Hypercholesterolemia
Smoking
Prior stroke
Prior myocardial infarction
Prior coronary artery bypass surgery
Clinical course
Left ventricular ejection fraction < 35% on echocardiography
Right ventricular dysfunction on echocardiography
Renal insufficiency (serum creatinine > 2.0 mg/dL)
Leukocytosis (white blood cell count > 18*10^9/L)
Adult respiratory distress syndrome
Respiratory failure as defined by a ratio of the arterial partial pressure of oxygen (P_aO_2) to fraction of inspired oxygen (F_iO_2) < 200 or mechanical ventilation > 7 days
Active radiographic evidence of pneumonia
Other documented infection

Long-Term Mortality

Long-term mortality was evaluated by examination of hospital medical records, national death registries, and through telephone contact. In-hospital mortality was defined as expiration during the hospital admission of iNO treatment. Deaths occurring during subsequent hospitalizations without iNO treatment were not counted toward in-hospital mortality, and mortality was only attributed to one encounter and one patient when multiple iNO encounters were present. The mean patient follow-up period was 2.9 $\pm$ 1.0 years.

Clinical Variables

Data on clinical variables were collected and are listed in Table 2.

Acquisition Cost of iNO

Charges for each iNO therapy encounter were calculated based on the charging practice of INO Therapeutics (AGA Healthcare, Clinton, New Jersey) between 2000 and 2003, and recalculated using the current 2005 charging practice. For the years 2000 to 2003, the charge to hospitals was $3,000 per 24 hours of therapy, up to a maximum charge of $12,000 per month, independent of