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Inhaled Pulmonary Vasodilator Therapy in Adult Lung Transplant: A Randomized Clinical Trial

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Abstract

Importance: Inhaled nitric oxide (iNO) is commonly administered for selectively-inhaled pulmonary vasodilation and prevention of oxidative injury following lung transplantation (LT). Inhaled epoprostenol (iEPO) has been introduced worldwide as a cost-saving alternative to iNO without high-grade evidence for this indication.

Objective: To investigate if iEPO will lead to similar rates of severe/grade-3 primary graft dysfunction (PGD-3) as the use of iNO after LT.

Design, Setting, and Participants: Health-system funded, randomized, blinded (to participants, clinicians, data managers and statistician), parallel-designed, equivalence clinical trial in 201 adult patients that underwent single or bilateral LT from May 30, 2017 to March 21, 2020.

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Interventions: Participants were grouped into five strata according to key prognostic clinical features and randomized per stratum to receive either iNO or iEPO at the time of LT via 1:1 treatment allocation. Allocated treatment was initiated before lung allograft reperfusion and continuously administered until cessation criteria were met in the intensive care unit.

Main Outcomes and Measures: The primary outcome was PGD-3 development at 24-, 48- or 72-hours after LT. The primary analysis was for equivalence using a two one-sided test (TOST) procedure (90% Confidence Interval, CI) with a margin of 19% for between-group PGD-3 risk difference. Secondary outcomes included duration of mechanical ventilation; hospital and intensive care unit lengths-of-stay; incidence and severity of acute kidney injury; postoperative tracheostomy placement; and in-hospital, 30-day and 90-day mortality rates. An intention-to-treat analysis was performed for the primary and secondary outcomes, supplemented by per-protocol analysis for the primary outcome.

Results: 201 randomized patients met eligibility criteria at the time of LT. In the intention-to-treat population, 103 received iEPO and 98 received iNO. The primary outcome occurred in 46 patients (44.7%) in the iEPO group and 39 (39.8%) in the iNO group, leading to a risk difference of 4.9% (TOST 90% CI, −6.4, 16.2; $P = 0.019$ for equivalence). There were no significant between-group differences for secondary outcomes.

Conclusions and Relevance: Among patients undergoing lung transplantation, use of iEPO was associated with similar risks for PGD-3 development and other postoperative outcomes compared to those that received iNO.

Trial Registration: ClinicalTrials.gov identifier: NCT03081052

Introduction

Inhaled nitric oxide (iNO) is administered after lung transplantation (LT) to promote lung-allograft function[1,2] by improving oxygenation and lowering pulmonary vascular resistance.[3–5,6] Consequently, iNO may help mitigate severe primary graft dysfunction (PGD grade-3 or PGD-3) development,[7] which is diagnosed within 72-hours after LT[8] and is strongly associated with short- and long-term mortality.[9,10] Although iNO is not approved by the U.S. Food and Drug Administration (FDA) for this indication, international guidelines support its use after LT.[8] In a recent survey of 74 LT centers worldwide, the primary inhaled pulmonary vasodilator (iPVD) was iNO in 73% (n=54 centers) followed by aerosolized or inhaled epoprostenol (iEPO) in 12% (n=9).[11]

Unfortunately, iNO cost exceeds millions of dollars annually for large healthcare systems nationwide and iNO is approximately seven-fold more expensive than iEPO.[12] Accordingly, iEPO has emerged as a cost-saving iNO-alternative at several institutions. Although similar anti-oxidative and vasodilatory properties of iEPO have been reported in LT,[13,14] evidence supporting use is not based on robust comparisons with iNO that evaluate for clinically-meaningful outcomes. Furthermore, available data interpretation is complicated by retrospective observational studies, differing epoprostenol formulations[15] and aerosol-generating devices,[16] and lack of standardized criteria for discontinuing either agent.

Given the serious nature of PGD-3 development and significant economic considerations of continued iNO use, clinician-investigators designed and conducted a randomized trial funded by the health system to determine if iEPO delivery would result in similar rates of PGD-3 and other outcomes after LT, compared with iNO.

Methods

Design

This was a parallel-designed, clinical trial that randomly assigned LT recipients ("participants") to receive either iNO or iEPO. This study is registered as part of the INSPIRE-FLO trial (Clinicaltrials.gov identifier: NCT03081052; see Supplement 1 for trial protocol). Two surgical populations were evaluated under this registration with separate, independent analysis plans. Analysis for the LT population is described here.

Funding

Research-related activities were funded through Duke University Health System. A separate process was established to ensure trial medication costs were covered by insurance providers. First, a blanket approval for trial enrollment was obtained for patients insured through the Centers for Medicare & Medicaid Services (CMS) before trial commencement. For other eligible patients, an enrollment request letter was sent to private insurers. The Institutional Review Board approved the protocol without a data safety monitoring board as both medications were on formulary and either could be used as standard-care. Adverse events were reviewed each quarter by the PI and research team while blinded to treatment assignment.

Participants

End-stage lung disease patients, 18-years and older, with insurance approval for enrollment were screened for eligibility upon transplant listing, approached for consent and randomized at the time of consent. Notable exclusions included combined-organ transplantation and presence of extracorporeal membrane oxygenation (ECMO) before LT. Given the variable duration from randomization to potential treatment initiation during LT, participants were included in the primary analysis if they were not withdrawn, did not die or develop changes to eligibility post-randomization.

Randomization and Blinding

Five randomization strata were created based on primary indication and single or bilateral lung-allograft transplantation. Within each strata, participants were assigned to receive either iNO or iEPO at the time of LT via 1:1 treatment allocation with block sizes of four. Randomization sequence was generated before trial commencement using nQuery Advisor® version 7 (Statsols, Inc., Cork, Ireland). Upon notification from the transplant coordinator that a participant would be undergoing LT, the research team would contact the study respiratory therapist and pharmacist. The pharmacist would access the password-protected randomization sequence list and prepare the allocated treatment.

Using an inline system for blinding iEPO and iNO delivery adopted from Preston et al.[17] (Supplement 2), blinding was preserved for all participants and clinicians involved in patient care. Additionally, allocated treatment was masked in the electronic record in a separate clinical documentation platform developed for this study (Maestro-Care®, Epic-Systems, Madison, WI). All research team members with database access (data managers) were blinded to treatment assignment. Following study completion, an independent statistician created a blinded-treatment assignment code for use during analysis and the study statistician remained blinded to the assignment until all analyses were completed.

Intervention

A blinded 50-millilter syringe solution of either 5% sodium chloride (if randomized to iNO) or 30,000 nanograms/ml epoprostenol (Veletri®, Actelion Pharmaceuticals, South San Francisco, CA) was prepared by the study pharmacist. Epoprostenol syringe-concentration was based on standard compounding by the pharmacy department. The study respiratory therapist would obtain the syringe from pharmacy, verbally confirm the solution identity, and place the syringe in a dedicated refrigerator. Fifteen minutes before reperfusion of the first transplanted lung, the study respiratory therapist would initiate the treatment in the operating room. Participants randomized to iNO (iNOMax®, Mallinkrodt Pharmaceuticals, St. Louis, MO) would continuously receive 20 parts-per-million while the iEPO group would continuously receive 50 nanograms/kg/min (ideal body weight) delivered using a syringe pump and vibrating mesh aerosolizer (Aerogen Pro-X®, Galway, Ireland). iEPO dosing derived from a dose-response study that displayed improved oxygenation between 10–50 ng/kg/min in acute respiratory distress syndrome[18] and has been adopted at multiple institutions for previous studies.[14,17,19–22]

After LT, the study therapist accompanied the clinical-care team to the ICU and ensured appropriate treatment delivery and blinding. In the ICU, a non-study respiratory therapist then assumed direct patient care. The study therapist remained immediately available to manage treatment delivery and was notified to wean each treatment by protocol once discontinuation criteria were identified (Supplement 1).

Standardized Care for Lung Transplantation

Standardized care for LT management at our institution, including intensive care, infection prophylaxis and immunosuppression, has been reviewed.[23] Relevant protocols for mechanical ventilation (Supplement 1) and ECMO management (Supplement 2) are included.

Outcomes

The primary outcome was PGD-3 development based on daily grading assigned at 24-, 48-, or 72-hour timepoints after ICU arrival following LT. Based on PGD guidelines,[8] grade-3 is diagnosed by poor systemic oxygenation (defined by *p*artial pressure of arterial oxygen-to-*f*raction of inspired oxygen, PaO_2:FiO_2 < 200 or ECMO use) and radiographic evidence for lung-allograft edema.[8]

Secondary outcomes included duration of mechanical ventilation measured from ICU arrival to endotracheal extubation, censored for those that underwent postoperative tracheostomy placement. Acute kidney injury (AKI) was determined by the Kidney Disease-Improving Global Outcomes (KDIGO) criteria (Supplement 2) up to seven days post-LT based on studies that have supported iEPO[24] and iNO[25] for renal protection. Other outcomes included hospital and ICU lengths-of-stay (LOS) and early postoperative mortality (in-hospital, 30-days, 90-days). Additionally, we compared daily average values for mean pulmonary arterial pressures between groups through postoperative day 3.

Statistical Methods

The statistical analysis plan (Supplement 1) is written in accordance with journal guidelines.[26] Analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

The trial was designed to demonstrate clinical equivalence between iEPO and iNO by a prespecified lower and upper bound around the PGD-3 outcome measure. The margin of equivalence was set to 19% with an anticipated PGD-3 incidence of 30% for the iNO group based on previous PGD-3 event rates that used the first 72-hours after LT as the primary outcome timeframe.[7,10,27–30] PGD-3 assessment was performed while participants remained in the hospital and loss to follow-up was not factored into sample-size determination. Thus, 200 participants allocated 1:1 would be sufficient to establish equivalence for the prespecified margin at 80% power. Alpha was controlled at 0.05 for all comparisons. Two one-sided tests (TOST) were used for primary outcome analyses while utilizing two-sided hypothesis testing for secondary outcomes.

An intention-to-treat analysis was planned for the primary and secondary outcomes, supplemented by per-protocol analysis for the primary outcome. Baseline characteristics were summarized for each treatment group and reported as mean (standard deviation, SD) or median (interquartile range, IQR) for continuous variables and as count (%) for categorical ones. Summaries were used to assess randomization performance and protocol adherence. Using the TOST procedure, the primary outcome was determined by calculating the point estimate and corresponding 90% confidence intervals, CI, for the risk difference between iEPO and iNO. If the CI were contained inside the equivalence margin, then there would be sufficient evidence to conclude that PGD-3 rates in each group would be similar ($P<0.05$). Relative risk, RR, estimates for PGD-3 development if treated with iNO compared with iEPO (95% CI) were reported. Based on baseline characteristics, the balance of patient factors was evaluated between treatment groups. All covariates meeting $P<0.15$ association between treatment groups were considered for variable selection to build a stepwise, multivariable regression model for PGD-3 to adjust the treatment difference for these potential confounders. Secondary outcomes were assessed for treatment differences under typical null hypothesis-utilizing univariable effect estimates and corresponding two-sided 95% CI. Binary secondary outcomes (tracheostomy, AKI, mortality) were assessed via risk differences and RR, while continuous secondary outcomes (ICU and hospital LOS) were assessed via risk differences and mean ratios estimated from log-linear regression models. Kaplan-Meier point estimates (95% CI) were used to determine mechanical ventilation duration censored for postoperative tracheostomy placement.

Finally, a *post-hoc* analysis was performed to determine overall and between-group PGD-3 rates using two commonly-reported sub-intervals of the 72-hour outcome timeframe: 48- or 72-hours[9,29] and 72-hours alone.[31]

Results

Population

From May 29, 2017 to March 21, 2020, 332 patients were screened. Of these, 112 patients did not meet eligibility criteria during screening, where 28 patients (8.4%) met exclusion criteria and 84 (25.3%) were eligible but not enrolled due to various reasons (Figure 1). Of 220 randomized participants, 19 (8.6%) developed changes to eligibility before they could receive the allocated treatment (8 needed ECMO before LT, 4 were withdrawn-by-physician for clinical deterioration, 3 were withdrawn for insurance denial, 3 were awaiting LT at time of study completion, and 1 died), leaving 98 patients who were allocated to the iNO group and 103 to the iEPO group (n=201). Final 90-day follow-up for mortality was performed on June 19, 2020.

Baseline and clinical characteristics for participants and organ-donors in the intention-to-treat analysis are shown (Table 1). Common indications for LT were restrictive (62.3%) and obstructive diseases (20.9%), which are proportionally consistent with the 2016 LT registry report.[32] There were 173 participants (86.1%) who underwent bilateral LT and 28 (13.9%) for single LT. Indications for single or bilateral LT were similar between treatment groups, indicating success of the stratified randomization.

For donor characteristics, donor-to-recipient sex mismatch was observed in 20 participants (20.4%) in the iNO group and in 34 (33.0%) in the iEPO group with a predominance of male donor-to-female recipient mismatch for both groups.

Intervention

Median (IQR) duration from randomization to treatment was 5-days (1, 20-days). Once initiated, allocated treatment durations, blood transfusion or ECMO support were similar between groups (Table 2). Delayed chest closure was observed in 15 patients (15.3%) who received iNO and in 7 (6.8%) who received iEPO (P=0.053).

Outcomes

In the unadjusted intention-to-treat analysis, PGD-3 incidence was 39.8% (n=39) in the iNO group and 44.7% (n=46) in the iEPO group for a risk difference of 4.9% (90% CI, −6.4%, 16.2%; P=0.019 in support for equivalence). The results of the adjusted intention-to-treat analysis using a stepwise data-driven, model-building approach (Supplement 3, eTable 1) and per-protocol analysis confirmed those of the unadjusted intention-to-treat analysis (Figure 2).

For secondary outcomes (Table 3), there were no significant between-group differences for mortality, AKI, tracheostomy placement, LOS or duration of mechanical ventilation censored for tracheostomy placement (Supplement 3, eFigure 1). No important differences

were found in adverse events (Supplement 3, eTable 2) or daily mean pulmonary arterial pressures (Supplement 3, eFigure 2).

Post-hoc analysis—Using the intention-to-treat population, the PGD-3 incidence at 48- or 72-hours was 26.5% (n=26) in the iNO group and 28.2% (n=29) in the iEPO group, for a risk difference of 1.6% (90% CI, −8.8%, 12.0% for equivalence). The PGD-3 incidence at the 72-hour mark was 16.3% (n=16) in the iNO group and 21.3% (n=22) in the iEPO group for a risk difference of 5.0% (90% CI, −4.5%, 14.6% for equivalence).

Discussion

In this trial of adult patients undergoing LT who prophylactically received iPVD to promote lung-allograft function, iEPO was associated with similar PGD-3 development as seen with iNO. Furthermore, no significant between-group differences were observed in durations of mechanical ventilation, LOS, tracheostomy and AKI incidences, or mortality up to 90-days.

Financial support for this study originated from the large economic impact of iNO use in this population on the health system. While specific contract-pricing is not disclosed, based on 2017 pricing, the cost-per-hour in a 70-kg adult for Veletri® was $6.52 while the non-contracted price for iNOmax® was $220.46.[12] While contract pricing may lower the hourly cost, the contract cost-per-hour of iNO remained 7-fold more than that of iEPO at our institution. In another study, McGinn reviewed 98 cardiothoracic surgical patients and found the median iEPO cost-per-patient was also seven-fold higher cost with iNO ($364 [IQR, $226-$865] vs. $2,563 [IQR, $1875-$8625], respectively; $P<0.01$).[33] While costs vary between institutions, the annual estimated iEPO expenditures can range from $200,000-$1,000,000 while that of iNO can exceed $3,000,000-$8,000,000.[12]

To our knowledge, this is the largest randomized trial comparing iEPO to iNO after adult LT using the PGD-3 outcome, which is diagnosed within an established timeframe after LT. PGD-3 may be modified through lowering of the pulmonary vascular resistance and limiting oxidative injury of the lung allograft. PGD-3 development can be devastating for long-term functional status with increased risk for redo LT from chronic lung-allograft dysfunction.[10] Benefits of iNO for PGD-3 prevention through prophylactic use were reported in a placebo-controlled trial where iNO was initiated before lung-allograft reperfusion, discontinued within 48-hours, and was associated with lower PGD biomarkers and two-fold lower PGD-3 incidence compared with placebo (45% versus 17%, $P<0.035$).[7] These authors defined PGD-3 development *within 72-hours* after LT using radiographic evidence of allograft edema, P:F ratio < 200, and no other cause for allograft dysfunction (i.e., anastomotic venous obstruction, infection or cardiogenic allograft edema).[7] Where our study implemented clinical protocols to wean the allocated iPVD when indicated, this study utilized a fixed 48-hour duration. Interestingly, we found similar between-group median durations for postoperative iPVD use that approximated 48-hours (Table 2).

Equivalence testing was chosen, rather than noninferiority alone, as both medications are used in LT centers worldwide and guidelines support use of either medication to promote allograft function.[34] The choice of the margin was based on the potential loss

of relative efficacy that was acceptable with iNO in return for non-efficacy advantages with iEPO. Thus, considerations encompassed risk differences of previous studies, powering for an important outcome and feasibility in accomplishing the study based on annual operations. Additionally, the 2016 FDA guidance document for noninferiority trials was reviewed, which endorsed using a margin that was less than the risk difference of best-available evidence between active control (i.e., iNO) and placebo.[35] FDA guidance was also reviewed for equivalence testing using the TOST procedure and allowable margin selection up to 20%.[36] Thus, the prespecified equivalence margin for this study satisfied these considerations.

Bias was minimized in this study through concealed allocation, analysis by randomized assignment, and medication blinding to participants, clinicians, data managers and statistician. Performing an appropriately powered and designed prospective investigation in this population is pragmatically challenging as most operations often occur at night, which creates logistical challenges for implementation of research-related activities. Furthermore, changes in clinical culture to adopt iEPO as a potential iNO alternative was critical for the successful implementation of a parallel-design with clinician blinding. In fact, protocol non-adherence occurred in only a single participant who was allocated to iEPO, switched to iloprost (long-acting prostacyclin) to accommodate a procedure, then transitioned back to iEPO.

Importantly, this study was funded through the health system without external support and medication costs were remunerated through insurance providers in the same manner as non-trial patients as both medications were standard-care. While blanket approval for CMS patients was obtained, private insurers were contacted individually, resulting in 58 eligible patients who were denied enrollment (Figure 1). Three of these were denied after an initial approval allowed for randomization. Furthermore, a separate documentation platform was developed to facilitate medication blinding during clinical-care and unblinding for medical billing after participant hospital discharge.

After randomization, participants who were not withdrawn for clinical deterioration, insurance denial, or death, were included in the intention-to-treat analysis. Modification of a classic intention-to-treat analysis has been previously described in trials of other critically-ill populations[37] and those undergoing other cardiothoracic operations.[38] Furthermore, given the standard use of iNO or iEPO during LT, analyzing all participants “as randomized” without iPVD blinding and risking potential for cross-over to the non-randomized treatment could have led to significant interpretation bias. Post-randomization changes to eligibility before LT mainly included new ECMO support, which was an established exclusion criteria since pre-LT ECMO support routinely continued after LT and would have confounded PGD-3 assessment.

A *post-hoc* analysis was performed to evaluate for PGD-3 development using two validated sub-intervals of the 72-hour assessment timeframe.[9,29,31] Compared with overall PGD-3 rates for the primary outcome (42.2%), lower rates were demonstrated at 48- and 72-hours (27.4%, consistent with a previous report of 30% using this timeframe[29]) and at 72-hours (18.9%). The first 24-hours was included in the primary outcome definition as the

allocated treatment could be weaned during this early postoperative period. In fact, 25% of participants were weaned by 31-hours after ICU arrival. Thus, evaluating the primary outcome at 48- or 72-hours while excluding the 24-hour mark could have potentially resulted in missed events in the early post-LT period related to interventions. Thus, we were able to capture all participants that experienced PGD-3 while receiving allocated treatment. Importantly, between-group PGD-3 risk differences at each sub-interval were similar to that of the intention-to-treat analysis, suggesting similar between-group effects on PGD-3 development at these differing timepoints along the 72-hour window.

Limitations

This study has several limitations. Although this study represents one of the largest randomized perioperative clinical trials in adult LT to date, it was of moderate size and powered for equivalence between treatment groups for the primary outcome. Second, the prespecified equivalence margin was based on a range of incidences that may have been considered too large. While confidence intervals for the RR of developing PGD-3 with iEPO versus iNO included the null hypothesis for unadjusted, adjusted and per-protocol analyses, the risk difference point estimate favored iNO in all three analyses. Thus, iEPO could conceivably be clinically-inferior while simultaneously meeting the statistical criteria for equivalence. While this is a potential interpretation, the current study represents the best available randomized evidence and suggests no between-groups differences were observed for PGD-3 development. Third, given the complexity of risk factors in this patient population, and the anticipation that the randomization would balance most potential confounders, an adjustment model was not prespecified. Instead, a stepwise data-driven, model-building approach was performed to adjust for significant outcome-effect modifiers. While this data-driven approach may not account for all potential sources of confounding, it does account for the most significant of them, and ones that would have been strong enough to bias our findings. For example, delayed chest closure, which heralds a more complex clinical course, occurred more often in the iNO group and was identified as a PGD-3 effect modifier and used to adjust the intention-to-treat analysis. Fourth, given the unique funding mechanism, a multicenter investigation could not be supported. Fifth, this study was not placebo-controlled. However, iPVD use was part of standard-care at our institution and placebo would have led to considerable cross-over to the treatment arm, thus complicating the interpretation between intention-to-treat and per-protocol analyses. Sixth, while prophylactic iPVD administration is part of our standard-care, this practice is not universal and some high-volume LT centers may selectively initiate iPVD in high-risk patients or after lung-allograft reperfusion injury. Nevertheless, high-risk patients were represented in this study and balanced between groups. Finally, this report was limited to 90-day outcomes and 1-year follow-up with a cost-effectiveness analysis is underway.

Conclusions

Among patients undergoing LT, use of iEPO was associated with similar risks for PGD-3 development and other outcomes compared to those that received iNO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Study data were collected and managed using REDCap™ hosted at Duke University.

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Author access to data. KG and MCW had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. MCW conducted and was responsible for the data analysis.

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Keypoints

Question:

In adult patients who receive inhaled pulmonary vasodilators during lung transplantation (LT), is there a difference in the rates of severe primary graft dysfunction (PGD-3) between those that receive inhaled epoprostenol (iEPO) and those that receive inhaled nitric oxide (iNO)?

Findings:

In this randomized clinical trial of 201 LT recipients, PGD-3 determined at 24-, 48- or 72-hours after LT occurred in 46 (44.7%) receiving iEPO and in 39 (39.8%) receiving iNO. This 4.9% risk difference (90% CI, −6.4, 16.0) was included within the margin to favor equivalence.

Meaning:

PGD-3 development after LT was similar between iEPO and iNO groups.

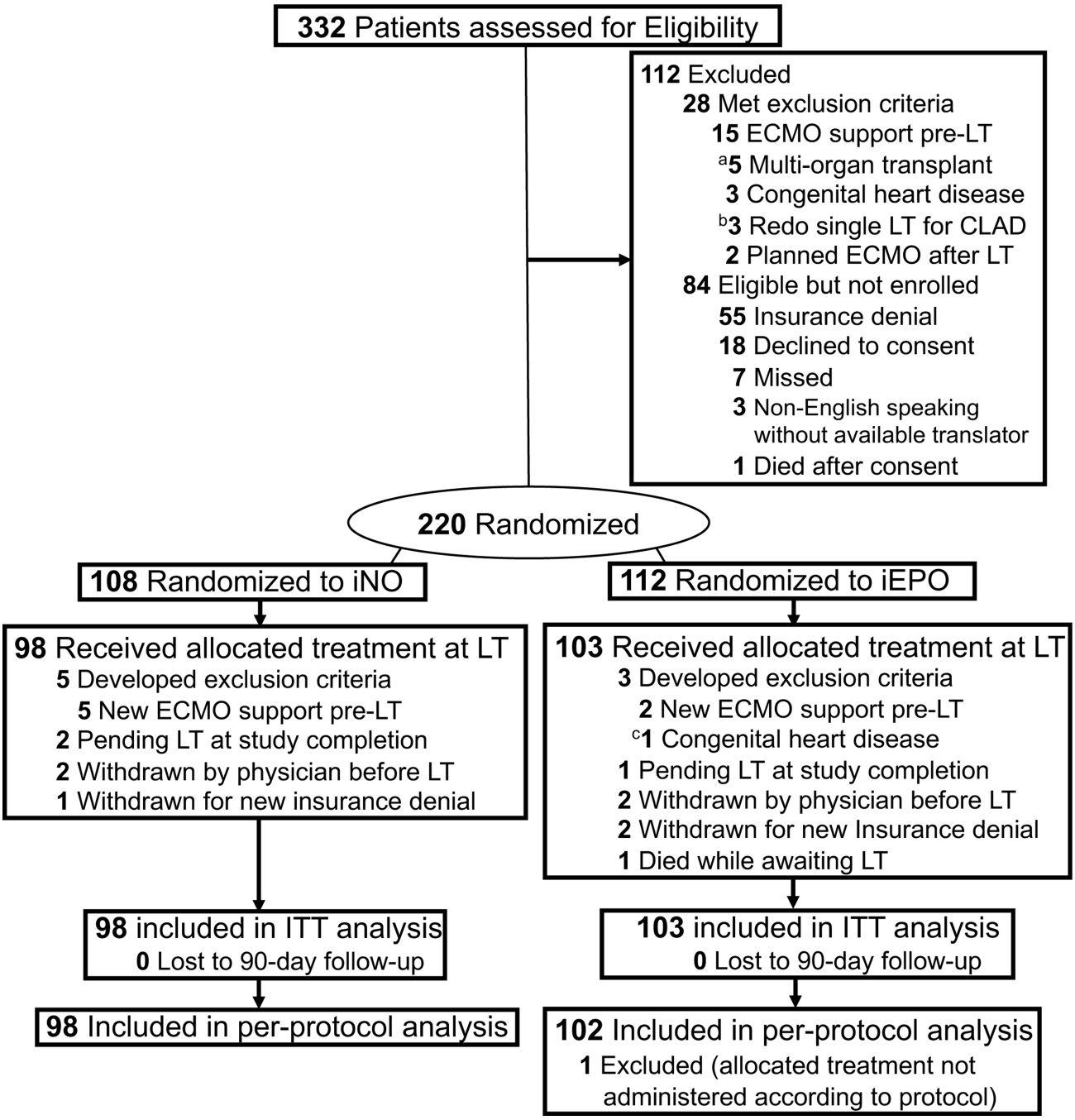


Figure 1. Flow of Participants in a Study of Inhaled Pulmonary Vasodilators for Adult Lung Transplantation.

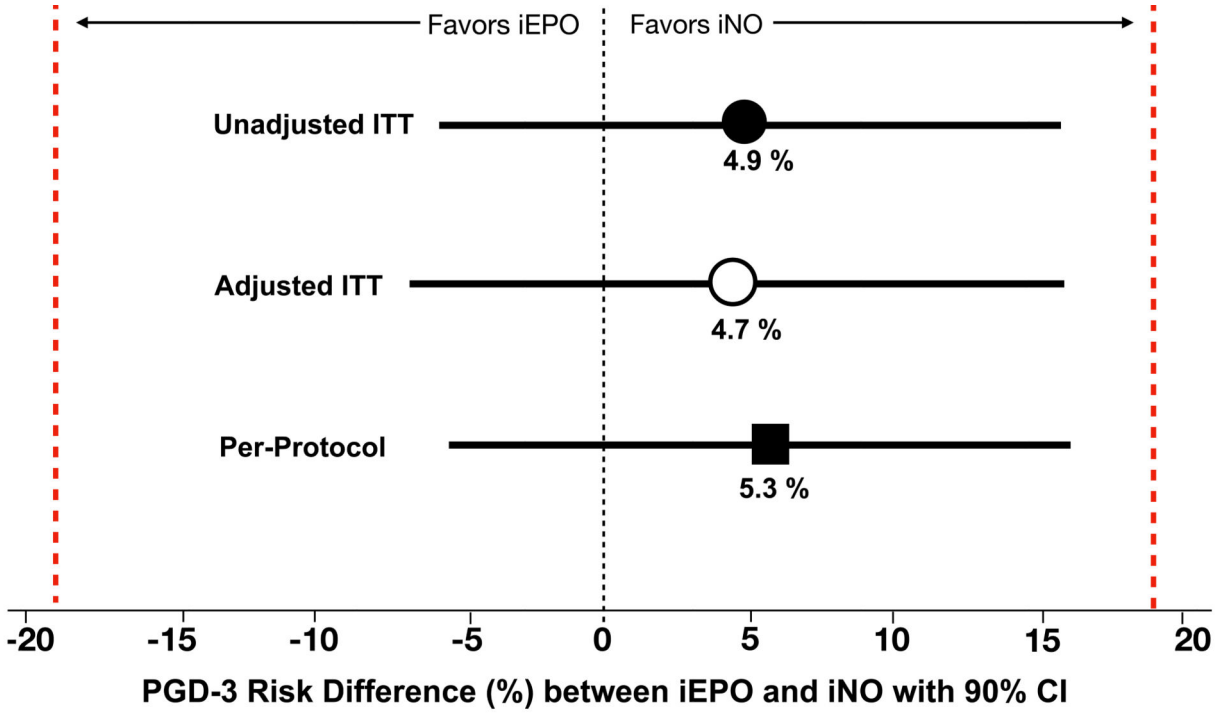
In all analyses, patients were analyzed according to their randomized group. Participants were excluded from the intention-to-treat analysis if they were withdrawn, developed exclusion criteria after randomization, or remained on the LT list and were not transplanted. Those that received the allocated treatment at the time of LT were included in an intention-to-treat analysis. Study enrollment was completed once sample-size was achieved. None of the participants were lost to 90-day follow-up.

[a]Multiple organ transplantation included 1 patient for lung-kidney and 4 patients for lung-liver.

[b]Patient with diagnosis that did not fit one of the five randomization strata

[c]Ineligible for enrollment, consented and randomized, then ineligibility was noted before LT.

CLAD, Chronic lung allograft dysfunction; ITT, Intention-to-treat; LT, Lung transplantation



Analysis	Number/Total Number (%) iNO	iEPO	[a]Risk Difference, % (90% CI)	[b]RR (90% CI)	[b]RR (95% CI)
ITT	39/98 (39.8%)	46/103 (44.7%)			
Unadjusted			4.9 (-6.4, 16.2)	0.89 (0.68, 1.17)	0.89 (0.64, 1.23)
[c]Adjusted			4.7 (-7.2, 16.5)	0.94 (0.74, 1.20)	0.94 (0.70, 1.26)
Per-Protocol	39/98 (39.8%)	46/102 (45.1%)	5.3 (-6.0, 16.6)	0.88 (0.67, 1.16)	0.88 (0.64, 1.22)

Figure 2. Risk differences and relative risks of PGD-3 development between iNO and iEPO treatment groups.

To determine the presence of clinical equivalence between iNO and iEPO, a lower and upper bounds of −19% and +19% was prespecified (red lines).

[a]Risk difference is the absolute difference between PGD-3 rates between groups and is determined by the two one-sided test (TOST) procedure. Setting α at 0.05 and testing the upper and lower bounds separately, equivalence is concluded only if both tests are significant. To transform this procedure into a single confidence interval, 1–2α (90%) is used and the TOST CI becomes the intersection of the two one-sided confidence intervals. A more conservative 95% CI (1-α) was determined and also demonstrated exclusion of the lower and upper bounds of the margin in support of equivalence for the unadjusted ITT (−8.6%, +18.3%), adjusted ITT (−9.5%, +18.8%) and per-protocol (−8.2%, +18.8%) analyses.

[b]Relative risk, RR, is the risk of developing PGD-3 if treated with iNO compared with iEPO.

[c]Multivariable logistic regression adjusting for delayed chest closure and donor-recipient sex mismatch from the selected model (Supplement 3, eTable 1). Risk difference and RR are derived from the multivariable logistic regression model. Differences between adjusted and unadjusted risk difference and RR are due to the difference in comparing two patients in the

adjusted analysis with the same sex-mismatch and chest closure status. However, number of events and their distribution between the unadjusted and adjusted analyses remain the same. CI, Confidence interval; iEPO, Inhaled epoprostenol; iNO, Inhaled nitric oxide; ITT, Intention-to-treat.

Table 1.

Baseline Participant Characteristics

	iNO (N=98)	iEPO (N=103)
Patient Demographics and History		
Age, years	64 (54, 68)	64 (51, 69)
Sex, male	59 (60.2%)	70 (68.0%)
Race		
Caucasian/White	83 (84.7%)	91 (88.3%)
African American	12 (12.2%)	9 (8.7%)
Other	3 (3.1%)	3 (2.9%)
BMI	25.0 (22.1, 26.7)	26.0 (22.8, 27.3)
HTN	48 (49.0%)	43 (41.7%)
PH Diagnosis	42 (42.9%)	54 (52.4%)
Severity of PH		
Mild	6 (6.1%)	7 (6.8%)
Moderate	29 (29.5%)	33 (32.0%)
Severe	7 (7.1%)	14 (13.6%)
DM (Types 1 or 2)	17 (17.3%)	25 (24.3%)
COPD	34 (34.7%)	45 (43.7%)
[a]Preoperative LVEF (%)		
Normal (≥ 50%)	94 (95.9%)	100 (97.1%)
Mild Dysfunction (40%−49%)	0 (0.0%)	1 (1.0%)
Moderate Dysfunction (30%−39%)	0 (0.0%)	1 (1.0%)
Previous Sternotomy for Cardiac Surgery	4 (4.1%)	2 (1.9%)
Previous Lung Transplant	6 (6.1%)	4 (3.9%)
Lung Allocation Score	42.0 (36.9, 51.9)	42.8 (37.2, 52.4)
Common Indications for Lung Transplant.		
Group A - Obstructive lung disease	21 (21.4%)	21 (20.3%)
Group B - Pulmonary vascular disease	2 (1.9%)	1 (1.0%)
Group C - Infectious lung disease	8 (8.2%)	15 (14.6%)
Group D - Restrictive lung disease	63 (64.2%)	63 (61.2%)
[b]Other	4 (4.1%)	3 (2.9%)
Preoperative Laboratory Values		
Estimated GFR (ml/min)	85 (70, 98)	88 (75, 100)
Hemoglobin (g/dL)	12.30 (1.65)	12.57 (1.73)
Creatinine (mg/dL)	0.9 (0.7, 1.0)	0.9 (0.7, 1.0)
Class 1 PRA > 0	17 (17.3%)	17 (16.5%)
Class 1 PRA % (among those >0)	17 (7, 75)	29 (17, 57)
Class 2 PRA > 0	13 (13.3%)	13 (12.6%)

	iNO (N=98)	iEPO (N=103)
Class 2 PRA % (among those >0)	38 (26, 49)	30 (22, 40)
Right Heart Catheterization Values		
Cardiac Index (L/min/m^2)	2.8 (2.5, 3.2)	2.9 (2.7, 3.3)
Mean PAP (mm Hg)	22.8 (18.3, 27.7)	24.7 (20.0, 29.7)
Procedural Characteristics		
[c]Bilateral Lung Transplantation	84 (85.7%)	89 (86.4%)
Obstructive Lung Disease	26 (26.5%)	31 (30.1%)
Restrictive Lung Disease	52 (53.1%)	53 (51.5%)
Pulm. Vascular Disease	2 (2.0%)	1 (1.0%)
Other Diagnosis[d]	4 (4.1%)	4 (3.9%)
[c]Single LT – Restrictive Lung Disease	14 (14.3%)	14 (13.6%)
Concurrent Cardiac Operation	7 (7.1%)	7 (6.8%)
Intraoperative CPB used	19 (19.4%)	19 (18.4%)
Intraoperative ECMO Used	33 (33.7%)	27 (26.2%)
Ischemia time, Single LT only, minutes	325 (304, 353)	325 (261, 340)
[e]Ischemia time, 2nd Lung only, minutes	395 (349, 489)	432 (352, 495)
[f]Use of Transmedics OCS™/EVLP	4 (4.1%)	3 (2.9%)
Donor Characteristics		
Age, years	35 (26, 46)	35 (27, 47)
Sex donor-to-recipient mismatch		
Matched	78 (79.6%)	69 (67.0%)
Female Donor-to-Male Recipient	6 (6.1%)	16 (15.5%)
Male Donor-to-Female Recipient	14 (14.3%)	18 (17.5%)
Race		
Caucasian/White	72 (73.5%)	74 (71.8%)
African American/Black	16 (16.3%)	17 (16.5%)
Other	10 (10.2%)	12 (11.7%)
[g]BMI of donor-recipient % mismatch	−4.5 (−20.4, 10.0)	−7.5 (−20.3, 7.2)
Donor PaO_2: FiO_2 ratio	443 (396, 494)	425 (378, 495)
Donor cigarette use > 20 pack years	11 (11.5%)	10 (9.7%)
Donation after Cardiac Death	10 (10.2%)	13 (12.6%)
Donation after Brain Death	88 (89.8%)	90 (87.4%)
Cause of Brain Death		
Anoxia	33 (33.7%)	30 (29.1%)
CVA/Stroke	26 (26.5%)	29 (28.2%)
Head Trauma	37 (37.8%)	41 (39.8%)
CNS Tumor	1 (1.1%)	0 (0.0%)

	iNO (N=98)	iEPO (N=103)
Other	1 (1.1%)	3 (2.9%)

[a]Preoperative LVEF available in 94/98 patients in iNO group and 102/103 participants from iEPO group

[b]Includes diagnoses that were not otherwise classifiable under Group A-D

[c]Randomization strata are based on single or bilateral LT and primary diagnosis for LT

[d]Other Bilateral LT diagnosis in iNO group (N=4): Bronchiolitis obliterans syndrome (N=2), Occupational fiberglass exposure (N=1), Adult Respiratory Distress Syndrome (N=1);
Other Bilateral LT diagnosis in iEPO group (N=4): Bronchiolitis obliterans syndrome (N=2), Coal worker's pneumoconiosis (N=2)

[e]By convention, for Bilateral LT, the ischemia time of the second lung only is reported

[f]Organ care system (Transmedics OCS™) use during lung-allograft transport after donor harvest has shown promise in reducing PGD-3 rates.[39]

[g]Negative percent indicates recipient BMI is less than donor BMI.

BMI, Body mass index; CPB; Cardiopulmonary bypass; CNS, Central nervous system; CVA, Cerebrovascular Accident; ECMO, Extracorporeal membrane oxygenation; EVLP, Ex-vivo lung perfusion; LVEF, Left ventricular ejection fraction; GFR, glomerular filtration rate; OCS, Organ care system; PaO_2:FiO_2, Partial pressure of arterial oxygen-to-Fraction of inspired oxygen; PAP, pulmonary arterial pressure; PRA, panel-reactive antibody

Table 2.

Participant Characteristics Relevant to Outcome Determination after Treatment Exposure

Parameter	iNO (N=98)	iEPO (N=103)	*P*-value
[d]Duration of treatment, hours	45.7 (33.1, 102.6)	46.6 (30.4, 83.6)	0.43[a]
Delayed Chest closure	15 (15.3%)	7 (6.8%)	0.053[b]
[e]ECMO Present on ICU arrival	17 (17.4%))	16 (15.5%)	0.73[b]
[f]ECMO placed within 72 hours	7 (7.1%)	6 (5.8%)	0.70[c]
[g]PRBC transfusion, Units	2 (0, 4)	2 (1, 4)	0.62[a]

p-Value Key:

[a]Wilcoxon

[b]Chi-Square

[c]Equal Variance t-test.

[d]In the per-protocol population, iEPO group had n=102, with median duration of 46.6 hours (IQR, 30.7, 83.6) after LT before discontinuation of iEPO.

[e]ECMO placement between ICU arrival and 72-hours after LT.

[f]ECMO placement in the operating room during LT that continued into the intensive care unit

[g]Transfusion data missing for 1 iNO patient

ECMO, Extracorporeal membrane oxygenation; ICU, Intensive care unit; PRBC, Packed red blood cells

Table 3.

Secondary Outcomes

Outcome	iNO (N=98)	iEPO (N=103)	Risk Difference, % (95% CI)	[a] Relative Risk (95% CI)	*P*-value
Mortality					
30-Day	2 (2.0%)	1 (1.0%)	−1.0 (−4.0, 2.0)	2.10 (0.19, 22.81)	0.61
90-Day	4 (4.1%)	4 (3.9%)	0.2 (−6.0, 5.0)	1.05 (0.27, 4.09)	0.94
In-Hospital	5 (5.1%)	7 (6.8%)	1.7 (−5.0, 8.0)	0.75 (0.25, 2.29)	0.61
Tracheostomy	22 (22.4%)	29 (28.2%)	5.8 (−6.0 to 18.0)	0.80 (0.49, 1.29)	0.35
[b] AKI of any stage	72 (73.5%)	67 (65.0%)	−8.5 (−20.0, 5.0)	1.12 (0.93, 1.34)	0.23
[b] AKI stages 2 or 3	29 (29.6%)	24 (23.3%)	−6.3 (−18.0, 6.0)	1.26 (0.79, 2.00)	0.33
			[d] HL Location Shift (95% CI)	[e] Mean Ratio (95% CI)	
ICU LOS (days)	4 (2, 10)	4 (2, 10)	0 (−1, 1)	1.19 (0.76, 1.87)	0.45
Hospital LOS (days)	23 (16, 38)	23 (15, 38)	0 (−3, 3)	1.03 (0.75, 1.41)	0.86
Duration of mechanical ventilation (hours)					
[f] KM Median (95% CI) Estimates	19 (15, 24)	22 (17, 36)			0.75[g]

[a] Relative Risk (with p-values) of developing the outcome if participants receive iNO rather than iEPO.

[b] Kidney Disease-Improving Global Outcomes AKI grading include stages 1, 2 or 3 in ascending order of severity. AKI stage 2 and 3 are more commonly associated with poor outcomes after Lung Transplantation (LT) and AKI incidence is independent of PGD-3 occurrence.[40]

[d] Hodges-Lehmann non-normal difference estimator

[e] Mean ratio with *P*-values from log-linear models.

[f] Measured from 197 patients (four patients had pre-LT tracheostomy). For those that received postoperative tracheostomy, time-to-extubation interval was censored at the time of tracheostomy placement to avoid underestimating the distribution of time-to-end of mechanical ventilation.

[g] Log-rank *P*-value

AKI, Acute kidney injury; ICU, Intensive care unit; KM, Kaplan-Meier analysis; LOS, Length-of-stay.