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Inhaled nitric oxide therapy was not associated with postoperative acute kidney injury in patients undergoing lung transplantation

A retrospective pilot study

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Abstract

Inhaled nitric oxide (iNO) therapy is commonly used in lung transplantation (LT) recipients during the perioperative periods. However, previous studies report that the use of iNO may increase the risk of renal dysfunction. Post-LT acute kidney injury (AKI) can lead to critical situations, including prolonged intensive care unit or hospital stays and increased morbidity and mortality. Accordingly, the aim of this study was to investigate the relationship between iNO therapy and incidence of post-LT AKI in LT recipients.

The medical data of 36 patients who underwent LT surgery from January 2012 to July 2017 in a single university hospital setting were retrospectively collected and analyzed. Patients were divided into 2 groups: iNO (n = 14) and control (n = 19). The demographic data, anesthetic methods, complications, and perioperative laboratory test values of each patient were assessed. Patients were categorized according to changes in plasma creatinine (Cr) concentration levels within 48 hours after LT using Acute Kidney Injury Network criteria.

There was no significant difference in the occurrence ($P = .13$) and severity ($P = .9$) of post-LT AKI between iNO and control groups. The mean serum Cr levels after surgery were 0.91 ± 0.44 and 0.81 ± 0.37 mg/dL in the iNO and control groups, respectively ($P = .50$).

AKI plays a critical role in the prognosis of LT recipients. Our results revealed that iNO therapy was not associated with the incidence of post-LT AKI. Therefore, if iNO treatment is indicated, active use under close monitoring of renal function is recommended in LT-patients concerned about AKI after surgery.

Abbreviations: AKI = acute kidney injury, Cr = creatinine, LT = lung transplantation, NO = inhaled nitric oxide, NO_2 = nitrogen dioxide, PH = pulmonary hypertension, RV = right ventricle.

Keywords: acute kidney injury, inhaled nitric oxide, lung transplantation

1. Introduction

Acute kidney injury (AKI) occurs in approximately 50% to 70% of patients after lung transplantation (LT),[1,2] which is a crucial complication associated with short- and long-term prognosis of LT recipients. The majority of patients with AKI did not require dialysis but had significant association with chronic kidney disease and poor clinical outcome.[3,4] Thus, additional efforts were needed to reduce the incidence of AKI in LT patients. Several factors that affect renal dysfunction in LT recipients include old age, medical treatments (corticosteroids, immunosuppressive treatment, diuretics, and nephrotoxic antibiotics), associated comorbidities (diabetes, hypertension, and pulmonary hypertension), reduction in effective blood volume during perioperative periods (intraoperative and postoperative bleeding), and low systemic vascular resistance owing to anesthetic drugs.[5] Recently, there was a report that inhaled nitric oxide (iNO) therapy was related with the postoperative AKI.

The treatment of LT recipients with iNO during perioperative periods is one of the most important anesthetic strategies. The use of iNO has been shown to improve oxygenation by selectively reducing pulmonary vascular resistance and right ventricular filling pressure, and prevent reperfusion injury and graft dysfunction.[6,7] Conventionally, iNO has been used safely with clinically insignificant extra-pulmonary effects, including systemic vasodilation, methemoglobinemia, and decline of platelet function. Furthermore, it has been reported that iNO has an affirmative effect on renal, hepatic, and splanchnic perfusion.[8] However, despite short-term improvement of oxygenation and right ventricular function, previous study showed that iNO therapy failed to alter clinically important patient outcomes such as the length of ICU stay and overall mortality.[9] Ruan et al[10] reported that iNO therapy induced renal dysfunction and led to poor prognosis.

Post-LT AKI is a common complication and is associated with a worse outcome. Therefore, we sought to elucidate the

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relationship between iNO therapy and the incidence of AKI in patients undergoing LT, and evaluate its impact on postoperative complications, and kidney function.

2. Methods

This retrospective study was approved by the institutional review board (No. 05-2017-145) of Pusan National University Yangsan Hospital, South Korea.

The medical records from our transplantation database of 36 patients who had received LT from January 2012 to July 2017 at Pusan National University Yangsan hospital were reviewed. Baseline demographics, comorbidities, and medications that may affect kidney function and preoperative laboratory findings were extracted from the computerized medical records. Exclusion criteria were as follows: repeated LT, history of end-stage renal disease with hemodialysis, showing unstable vital signs (mean blood pressure < 60 mm Hg despite vasopressor infusion) within 48 hours after surgery, and lack of available data.

The enrolled patients had undergone surgery under general anesthesia with target-controlled infusion (TCI). A commercial TCI pump (Orchestra Base Primea, Fresenius Vial, France) was used for the effect-site TCI of propofol (50 mL Fresofol 2% inj.; Fresenius Kabi, Austria) and remifentanil (1 mg Ultiva inj.; GlaxoSmithKline, Belgium), by using infusion models for propofol and remifentanil[11] that was maintained with a BIS value of 40 to 60. Cis-atracurium was used as a muscle relaxant. Intraoperative monitoring of all patients involved electrocardiography, peripheral O_2 saturation, end-tidal CO_2 concentration, cerebral blood oxygenation, bispectral index, and invasive arterial monitoring via radial and femoral arteries. Subsequently, a pulmonary artery catheter (Swan-Ganz CCOmbo model: 744HF75, Edwards Lifesciences, Irvine, CA) was inserted via Advanced Venous Access Catheters (AVA High-Flow Devices, Edwards Lifesciences, Irvine, CA) and placed in the left internal jugular vein, and connected to a Vigilance monitoring system (Vigilance II monitor, Edwards Lifesciences, Irvine, CA), which allowed monitoring of stroke volume, stroke volume index, cardiac output, cardiac index, central venous oxygen saturation, and systemic vascular resistance index as parameters of fluid and circulatory management. During surgery, a crystalloid (Hartmann's solution, normal saline, or plasma solution-A) was administered when either the mean arterial pressure < 60 mm Hg or the urine output < 0.5 mL/kg/h. Packed RBCs were considered only to maintain the hemoglobin concentration of 10 g/dL or a hematocrit concentration of 25% to 30% depending on the decision of the attending anesthesiologist. After using the kaolin-activated thromboelastography (TEG 5000 series; Haemoscope, Skokie, IL) before recipient's lung was resected, during anastomosis, and after anastomosis of donor's lung to recipient was conducted, coagulation products were administered as needed. Pulmonary capillary wedge pressure was assessed to guide fluid management. Fluids were administered in order to maintain the pulmonary capillary wedge pressure between 6 and 15 mm Hg.

After the completion of surgery, patients were transferred to the intensive care unit (ICU) with intubation. Standardized postoperative care was provided to all patients with hemodynamic monitoring performed.

AKI in the postoperative period was diagnosed according to the Acute Kidney Injury Network (AKIN) criteria. Stage I was defined as an increase of serum creatinine (Cr) level from baseline of ≥ 0.3 mg/dL (normal reference range, 0.7–1.4 g/dL at our institution), or an increase from baseline range of 150% to −200%; stage II as an increase from baseline ranging from 200% to −300%; and stage III as an increase from baseline > 300%, or serum Cr level ≥ 4.0 mg/dL accompanied by an acute increase from baseline of ≥ 0.5 mg/dL, or requiring renal replacement therapy irrespective of other criteria.

2.1. Statistical analysis

Continuous variables were expressed as mean ± standard deviations and categorical variables as numbers and percentages. Baseline and intraoperative characteristics and variables for postoperative outcomes were compared using the *t*-test or the Mann–Whitney rank sum test for continuous variables, and the χ^2 test or Fisher's exact test for categorical variables.

All statistical analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC). A *P*-value < .05 was considered statistically significant. To confirm the adequacy of the number of subjects, the G*power software (version 3.1.9.3; Dusseldorf University, Dusseldorf, Germany) was used.[12]

3. Results

The flow diagram of patients through the study is shown in Figure 1. Of the 36 patients identified, we included only 33 patients who underwent LT. One patient underwent repeated surgery and 2 patients with missing data were excluded. Patients were divided into 2 groups: iNO (n = 14) and control (n = 19).

Patients' characteristics including age, body mass index, cause of LT, preoperative status, and coexisting disease are shown in Table 1. There was no significant difference in patients' characteristics. Preoperative laboratory data are shown in the following Table 2, which reveal no significant differences between the 2 groups including oxygen index and serum Cr.

Patients' perioperative factors including duration of anesthesia, estimated blood loss, total volume of fluid intake, volume of transfusion per blood product, and urine output are listed in Table 3. There was also no significant difference.

The mean serum Cr levels after surgery were 0.91 ± 0.44 and 0.81 ± 0.37 mg/dL in the iNO and control groups, respectively. There was no significant difference between the 2 groups. AKI occurred in 57.1% (n = 8) of patients in the iNO group and 31.6% (n = 6) in the control group as demonstrated in Table 4, which did not demonstrate any significant difference between the 2 groups. There was no difference in the incidence of AKI from the whole cohort and the severity of renal dysfunction among patients with postoperative AKI between the 2 groups. Duration of ICU stay and total hospital stay showed no difference between the 2 groups. Postoperative complications also did not vary between the 2 groups (Table 5). The result of post-hoc power analysis was determined to be 0.88 based on an α-alpha value of 0.05, total sample size of 33 and an effect size of 0.55.

4. Discussion

In this retrospective review of LT recipients, iNO therapy was not associated with postoperative incidence or severity of AKI. In addition, iNO therapy did not affect postoperative complications, ICU stay, or total hospital stay.

LT is established for patients with a variety of end-stage lung diseases to improve quality of life and prolong life expectancy.[13,14] Although it is a lifesaving measure, LT is associated with well-known postoperative complications that contribute to

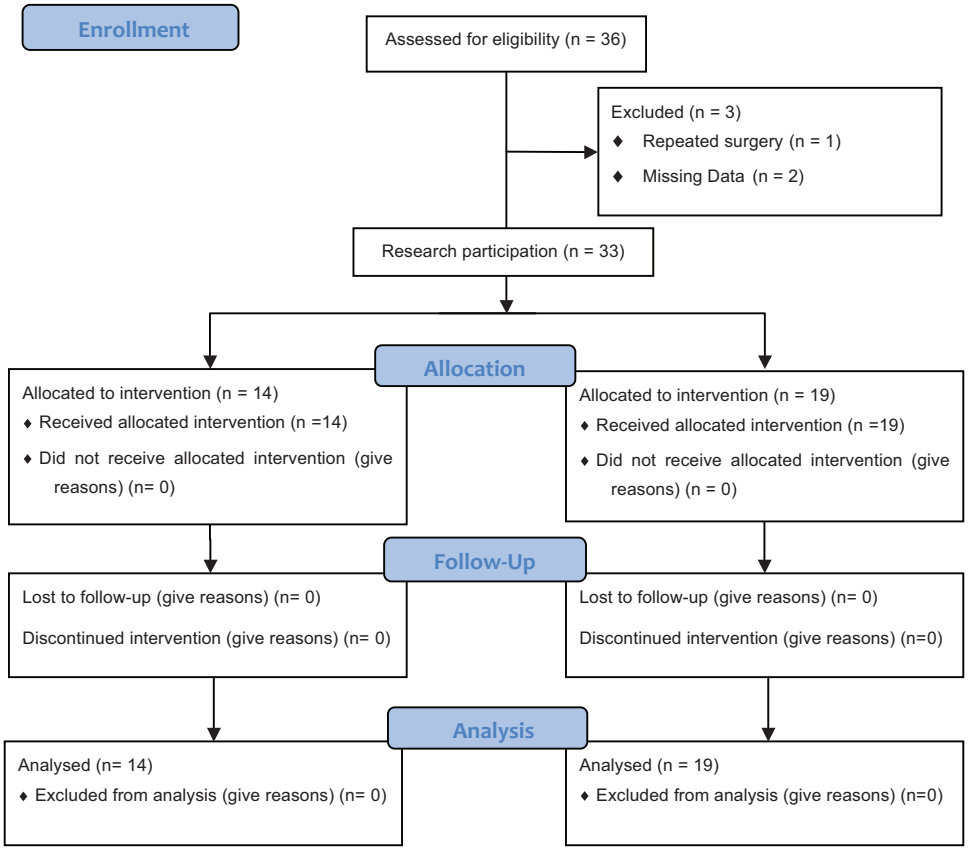

Figure 1. CONSORT flow diagram of this study.

critical morbidity and mortality.[13–15] Among them, postoperative AKI reduces survival rate of patient and graft.[16,17] Moreover, prolonged AKI and newly developed chronic kidney disease are important risk factors for long-term morbidity after LT.[18,19] In our study, the incidence of AKI after LT (81%) was higher than in other recent studies (50%–70%).[1,2] However, there was no need for renal replacement therapy following LT in our study. Renal replacement therapy after LT was reported around 10% in previous studies.[20,21]

Several factors[5,15,18] influenced the outcome of this study. Risk factors for the development of AKI after LT include sex, hypertension, diabetes mellitus, myocardial infarction, heart failure, and premorbid chronic renal disease, sepsis, and massive pulmonary embolism. In addition, the use of corticosteroids, immunosuppressive treatment, antibiotics, concurrent treatment with diuretics, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers, and renal artery occlusion because of thrombus or embolism is associated with perioperative AKI. Low systemic vascular resistance owing to anesthetic drugs, and reduction in effective blood volume affect renal

Table 1

Characteristics of patients undergoing lung transplantation.

	Inhaled NO (n = 14)	Control (n = 19)	*P* value
Age, years	56.0 (49.5–59.0)	58.0 (53.0–61.0)	.20
Sex (F/M)	5 (35.7)/9 (47.3)	7 (36.8)/12 (63.2)	.62
Height, cm	162.0 ± 10.08	163.5 ± 8.5	.62
Weight, kg	53.2 ± 10.4	57.4 ± 11.8	.30
Cause of lung transplantation			.66
Idiopathic pulmonary fibrosis	6 (42.9)	6 (31.6)	
Primary pulmonary hypertension	1 (7.1)	0	
Interstitial lung disease	7 (50.0)	13 (68.4)	
Pretransplant intubation	9 (64.3)	15 (78.9)	.25
Pretransplant ECMO	6 (42.9)	5 (26.3)	.56
Pretransplant CRRT	3 (21.4)	3 (15.8)	1
HTN	3 (21.4)	3 (15.8)	1
DM	4 (28.6)	3 (15.8)	1
IHD	0	2 (10.5)	1
With diuretics	1 (7.1)	1 (5.3)	.45
With insulin	0	2 (10.5)	1

Values are expressed as mean ± SD, number (%).

CRRT = continuous renal replacement therapy, DM = diabetes mellitus, ECMO = extracorporeal membrane oxygenation, HTN = hypertension, IHD = ischemic heart disease, NO = nitric oxide.

Table 2

Preoperative laboratory data in patients undergoing lung transplantation.

	Inhaled NO (n = 14)	Control (n = 19)	*P* value
Oxygen index	29.8 ± 21.8	32.5 ± 21.7	.39
Hb, g/dL	10.4 ± 2.5	10.6 ± 1.8	.75
PLT ($\times 10^3$/mL)	182.0 ± 102.9	150.6 ± 71.0	.31
Protein, g/dL	5.8 ± 1.3	6.1 ± 1.3	.64
Albumin, g/dL	3.1 ± 0.6	3.1 ± 0.6	.81
Creatinine, mg/dL	0.4 (0.4–0.7)	0.7 (0.4–0.9)	.26
Na, mEq/L	137.2 ± 4.6	135.4 ± 2.8	.16
K, mEq/L	4.1 ± 0.6	4.1 ± 0.4	.90

Values are expressed as mean ± SD or median (25th–75th percentile). Hb = hemoglobin, K = potassium, Na = sodium, NO = nitric oxide, PLT = platelet.

Table 3

Perioperative factors of patients undergoing lung transplantation.

	Inhaled NO (n = 14)	Control (n = 19)	*P* value
Anesthetic time, hours	13.6 ± 1.8	14.1 ± 1.8	.38
VA ECMO time, hours	6.0 (5.0–6.0)	6.0 (5.0–7.4)	.67
EBL, L	4.4 (2.0–9.2)	6.0 (2.0–8.8)	.97
Total fluid, L	8.9 (6.1–12.4)	8.1 (6.4–17.1)	.70
pRBC, pints	15.0 (9–28)	15.0 (6–21)	
FFP, pints	13.5 (5–15)	9.0 (4–14)	
Cryo, pints	22.5 (15–30)	20.0 (18–30)	
PLT, pints	16.0 (5–32)	16.0 (9–24)	
Pheresis, pints	3.0 (2–3)	4.0 (3–5)	
Urine, L	1.8 ± 1.0	2.3 ± 0.8	.17

Values are expressed as mean ± SD or median (25th–75th percentile).

Cryo = cryoprecipitate, EBL = estimated blood loss, FFP = fresh frozen plasma, NO = nitric oxide, PLT = platelet, pRBC = packed red blood cells, VA ECMO = venoarterial extracorporeal membrane oxygenation.

function of LT patients during perioperative periods. As most LT recipients are affected by multidrug-resistant bacterial infection such as *Pseudomonas aeruginosa* or cytomegalovirus infection/reactivation, antibiotic and antiviral treatments with possible nephrotoxicity are generally required. During the operation of LT and ICU stay, diuretics are usually administered to prevent post-reperfusion pulmonary edema and primary graft dysfunction. High-dose diuretics induce negative fluid balance, and result in electrolyte imbalance, ototoxicity, and prerenal AKI. Besides, patients undergoing LT often receive iNO therapy, which is used to treat acute respiratory distress syndrome and persistent pulmonary hypertension. It may affect the incidence of postoperative AKI.

The mechanism of iNO related AKI remains unclear. In a swine study, exposure of iNO appeared to generate renal tubular apoptosis.[22] In this report, renal resorption was significantly reduced by iNO, and may have triggered tubular and glomerular injury. In terms of nitric oxide metabolites, iNO elevates serum levels of plasma cyclic guanosine monophosphate (cGMP), nitrate, and nitrite.[23] These nitric oxide metabolites induce AKI via protein nitration and increased oxidative load.[24,25] In addition, considering the role of nitric oxide pathways in lung, oxidative injury due to highly oxidative nitrogen compounds may also induce iNO-related kidney injury. Reactive nitrogen species such as nitrogen dioxide (NO_2) are highly oxidative compounds that are generated when iNO is combined with high concentrations of oxygen in alveoli.[26] In patients with ARDS managed with iNO, serum concentrations of NO_2 show a positive association with the dose of iNO administered.[27] Systemically circulating NO_2 may induce cytotoxic effects in renal parenchymal cells.[28] Therefore, iNO therapy appears to trigger peri-operative AKI in patients after LT. Therefore, our study investigated the relationship between iNO therapy and postoperative AKI. However, our findings showed no significant difference in the risk of post-LT AKI ($P = .13$) between iNO and control groups and the severity of renal dysfunction ($P = .9$) also showed no difference between the 2 groups. Furthermore, ICU stay and time from surgery to discharge also did not vary between the 2 groups.

Table 4

Effect of NO inhalation on risk of AKI in patients undergoing lung transplantation.

	Inhaled NO (n = 14)	Control (n = 19)	*P* value
AKI	8 (57.1)	6 (31.6)	.14
AKIN stage			.15
0	6 (42.6)	13 (68.4)	
1	3 (21.4)	3 (15.8)	
2	4 (28.6)	2 (10.5)	
3	1 (7.1)	1 (5.3)	

Values are expressed as number (%).

AKI = acute kidney injury, AKIN = Acute Kidney Injury Network, NO = nitric oxide.

Table 5

Postoperative data of patients undergoing lung transplantation.

	Inhaled NO (n = 14)	Control (n = 19)	*P* value
Hb, g/dL	10.5 ± 1.4	10.4 ± 1.8	.93
PLT ($\times 10^3$/mL	126.3 ± 51.6	121.2 ± 52.6	.31
Protein, g/dL	4.9 (4.3–5.1)	5.0 (4.3–5.4)	.72
Albumin, g/dL	2.9 ± 0.4	2.7 ± 0.6	.30
Creatinine, mg/dL	0.9 ± 0.4	0.8 ± 0.4	.50
Na, mEq/L	138.4 ± 2.5	139.1 ± 4.3	.60
K, mEq/L	4.3 (3.7–4.4)	4.4 (4.2–4.6)	.35
ICU stay, days	19.5 (15.0–27.0)	20.0 (11.0–26.0)	.70
SOFA score	9.6 ± 4.3	12.8 ± 2.6	.05
APACHE II score	11.0 ± 5.1	11.6 ± 4.1	.78
Time from surgery to discharge, days	50.1 ± 39.4	64.7 ± 61.0	.31
Postoperative complication			.26
Cardiac complication	2 (14.3)	2 (10.5)	
Respiratory complication	1 (7.1)	2 (10.5)	
Neurologic complication	0	0	
Acute rejection	0	1 (5.3)	

Values are expressed as mean ± SD, number (%). Values are expressed as mean ± SD or median (25th–75th percentile).

APACHE = Acute Physiology and Chronic Health Evaluation, Hb = hemoglobin, ICU = intensive care unit, K = potassium, Na = sodium, NO = nitric oxide, PLT = platelet, SOFA = Sepsis-related Organ Failure Assessment.

There are several limitations in our present study. First, this is a single center retrospective study and with a small size, which appears to be insufficient to generalize the relationship between iNO and AKI. However, we controlled the differences in several factors[12,29,30] such as underlying diseases affecting renal function, preoperative medications, preoperative conditions such as intubation, application of ECMO or CRRT, preoperative blood tests and perioperative management, and found no differences between the 2 groups. Second, there was no standard protocol for administering iNO therapy, in the absence of unequivocal clinical decision-making for iNO use. The use of iNO therapy was mainly determined by the status of lung and without considering the renal status of the patients. Third, the optimal time to initiate and discontinue iNO therapy also remains ambiguous. All patients using iNO therapy during surgery continued with it until they received treatment in the intensive care unit, and discontinued depending on the patient's condition.

In conclusion, we found that the use of iNO during and after LT to control refractory hypoxemia and acute increase of pulmonary vascular resistance which may cause right ventricular dysfunction and hemodynamic instability, does not affect the incidence or severity of AKI. Therefore, if clinically indicated in LT patients at risk of AKI after surgery, active iNO treatment is recommended under close monitoring of renal function. In addition, as our study is limited by its retrospective design, we recommend further prospective randomized controlled multicenter studies as well as laboratory studies to investigate the association between iNO therapy and AKI.

Author contributions

Conceptualization: Hyun-Su Ri, Hyo Jung Son, Ju Yeon Kim, Yoon Ji Choi.
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Writing – original draft: Hyo Jung Son, Han Byeol Oh, Yoon Ji Choi.
Writing – review & editing: Hyun-Su Ri, Hyo Jung Son, Su-Young Kim, Ju Yeon Kim, Yoon Ji Choi.

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