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Assessing the nitric oxide efficacy in bilateral lung transplantation

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Abstract

Background. *One of the most frequent and severe complications in the early postoperative period in lung transplantation is primary graft dysfunction resulting from ischemia-reperfusion injury. There is evidence of the effectiveness of using inhaled nitric oxide in order to prevent such injury.*

Objective. *To assess the effectiveness of nitric oxide in the intra- and early postoperative period in bilateral lung transplantation.*

Material and methods. *We examined 43 patients who underwent bilateral lung transplantation at the N.V. Sklifosovsky Research Institute for Emergency Medicine in the period from 2012-2021. The patients were divided into two groups. The study group consisted of 23 patients, whose complex of treatment included the use of inhaled nitric oxide. Patients in the comparison group (n=20) received a standard therapy. The end points of the study were: the mechanical ventilation duration, the*

frequency of using extracorporeal membrane oxygenation and its duration, mortality, dynamics of oxygenation index, blood lactate level, pH, base deficiency.

Results. *The use of inhaled nitric oxide therapy in patients in the intra- and early postoperative period during lung transplantation improved the ventilation-perfusion ratio, as evidenced by an increase in the oxygenation index by 1.1 times (p=0.128) and 1.3 times (p=0.026) at 48 and 72 hours after surgery, respectively. Meanwhile, the frequency of using extracorporeal membrane oxygenation during surgery was found to decrease by 1.2 times (p=0.033), and that after surgery decreased by 1.4 times (p=0.474); the mechanical ventilation duration decreased by 1.4 times (p=0.042); the duration of extracorporeal membrane oxygenation decreased by 1.6 times (p=0.028); mortality reduced by 8%.*

Conclusion. *The use of inhaled nitric oxide therapy for lung transplantation had a positive effect on the intra- and early postoperative period, as indicated by an improvement in blood gas parameters, a reduction in the frequency and duration of veno-arterial extracorporeal membrane oxygenation, and the duration of mechanical ventilation.*

Keywords: lung transplantation nitric oxide, inhaled nitric oxide, intraoperative period, early postoperative period, primary graft dysfunction, ischemia-reperfusion injury

Conflict of interests Authors declare no conflict of interest

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COPD, chronic obstructive pulmonary disease

ECMO, Extracorporeal Membrane Oxygenation

FFP, fresh frozen plasma

iNO, inhaled nitric oxide

IRI, ischemia-reperfusion injury

LT, lung transplantation

MLV, mechanical lung ventilation

NO, nitric oxide

PAP, pulmonary artery pressure

PGD, primary graft dysfunction

VA-ECMO, veno-arterial extracorporeal membrane oxygenation

Relevance

Lung transplantation (LT) is the main surgical method for the treatment for end-stage lung diseases. One of the most common and severe complications in the early postoperative period is a primary graft dysfunction (PGD) of the lungs resulting from ischemia-reperfusion injury (IRI). According to the literature, the incidence of PGD makes 30%, while in 42% of cases it leads to death in the first month after the surgery [1-4].

Nitric oxide (NO) is a powerful endogenous vasodilator involved in the regulation of systemic and pulmonary vascular resistance [5, 6]. The discovery of the nitric oxide role in the pathogenesis of pulmonary circulation disorders has led to its use in the complex treatment of LT patients. Its inhalation contributes to the regional expansion of the pulmonary capillaries, an increase in the volume of blood passing through the ventilated alveoli, which leads to an improvement in the gas exchange. The main role of inhaled NO (iNO) is believed to be its effect on pulmonary vascular resistance. A number of authors have shown pathogenetically-grounded reasons for using exogenous iNO in this surgical intervention. In addition to the effect on the vascular tone, the use of iNO leads to an improved tissue perfusion, a decreased adhesion of

leukocytes and platelets to the vascular endothelium, and an increased antithrombogenic effect, which helps prevent the critical stage of the inflammatory reaction, and apoptosis [6, 7]. NO inhibits the expression of several inflammatory mediators, including interleukins, endothelin-1, and adhesion molecules [8-10]. These effects of nitric oxide determine the appropriateness of its use in PGD of the lungs [11–16].

Currently, there are experimental and clinical data indicating the ability of nitric oxide to reduce pulmonary hypertension and ischemia-reperfusion lung injury. However, the results of a number of conducted studies are contradictory regarding the efficacy of using nitric oxide to reduce the IRI severity. The lack of randomized clinical trials examining the efficacy of this treatment method in the intraoperative and early postoperative period in lung transplantation prompted us to conduct this study.

Purpose. To evaluate the efficacy of using nitric oxide in the intraoperative and early postoperative period in patients with bilateral lung transplantation to prevent a PGD development.

Material and methods

A retrospective clinical study included 43 patients who underwent bilateral lung transplantation in the period from 2012–2021 at the N.V. Sklifosovsky Research Institute for Emergency Medicine. The median age of patients was 33 (25-46) years. The patients were divided into two groups: the study group (23 patients), whose complex of the intraoperative and early postoperative treatment, included the use of iNO in addition to the standard therapy, and the comparison group that consisted of 20 patients who received the standard therapy during the operative intervention.

Indications for using iNO were lung transplantation, mean pulmonary artery pressure (PAP) >25 mm Hg, age 18-65 years. Patients were not included in the study if, due to their severe condition before transplantation, were on mechanical lung ventilation (MLV) or were connected to an extracorporeal membrane oxygenation (ECMO) machine.

Table 1 presents the general characteristics of the patients included in the study.

Table 1. General characteristics of patients

Parameters	Study group	Comparison group	p
Number of patients, n	23	20	-
Age, years Me (Q25;Q75)	31 (27;43)	30.5 (24;42)	0.756
Men, n (%)	12 (52.1)	10 (50)	0.887
Women, n (%)	8 (34.8)	8 (40)	0.724
Duration of the first graft preservation, min.	390(365;468)	385(318;470)	0.672
Duration of the second graft preservation, min.	578(501;630)	570 (515;630)	0.725

The groups were comparable in terms of age, gender, duration of graft preservation. The distribution of patients in both groups according to nosological forms before surgery is presented in Table 2.

Table 2. Structure of nosological forms

Nosological forms	Study group (n=23)	Comparison group (n=20)	p
Obstructive diseases ((COPD/emphysema, bronchiectasis, sarcoidosis (mean pulmonary artery pressure ≤30 mm Hg), lymphangioleiomyomatosis, bronchiolitis obliterans), n (%)	6 (26.1)	6 (30)	0.775
Vascular disease (idiopathic pulmonary hypertension, Eisenmenger syndrome), n (%)	2 (8.7)	15)	0.635
Cystic fibrosis, immunodeficiency syndromes, n (%)	10 (43.4)	9 (45)	0.920
Restrictive diseases (idiopathic pulmonary fibrosis, sarcoidosis with mean pulmonary artery pressure ≥30 mm Hg), n (%)	5 (21.7)	4 (20)	0.889

Note: COPD, chronic obstructive pulmonary disease

The number of patients with restrictive lung diseases in the groups was comparable.

Patients' evaluation before surgery was performed according to the protocol for examining a LT recipient. Anesthesia was performed according to the standard scheme. Infusion-transfusion therapy in the intraoperative period included the administration of crystalloid and colloid solutions, transfusion of blood components if hemoglobin fell below 80 g/L. In addition to allogeneic blood transfusion, the apparatus autotransfusion of erythrocytes was used. With the development of coagulopathy, fresh frozen plasma (FFP) was transfused. MLV was performed using Drager devices (in the Operating Room and in the Intensive Care Unit) in a mode that provided for individual selection of parameters. The parameters of mechanical ventilation and lung biomechanics were recorded in real time using a monitoring system. Central veno-arterial ECMO (VA-ECMO) was used in patients with uncontrolled hypoxemia, unstable hemodynamics, and increasing lactic acidosis.

For iNO-therapy, a certified NO–NO_2 gas mixture with iNO concentration of 1000 ppm (parts per million) was used. The iNO (20–40 ppm) was supplied into the inspiratory part of the respiratory circuit of the ventilator at a distance of 60–80 cm from the Y-shaped connector. Bedfont Scientific Ltd System (England) was used to ensure a low gas flow. The iNO volumetric flow rate (in mL/min) was set according to the required concentration and the readings of the electrochemical NO–NO_2 analyzer. The iNO therapy was started after the lung reperfusion. The mean iNO concentration was 30±1 ppm. The duration of the treatment by this method reached 2-4 days. In a number of cases (n=13), the iNO-therapy was discontinued after the anesthesia completion. The criteria for

discontinuation of iNO-therapy were: weaning the patient from VA-ECMO, oxygenation index over 150, hemodynamic stability.

The primary endpoint of the study was the oxygenation index dynamics (PaO_2/FiO_2) after the induction and completion of anesthesia, at 24, 48, and 72 hours after surgery. Secondary endpoints were MLV duration, VA-ECMO frequency, VA-ECMO duration, blood lactate levels, base deficit for pH before and after the anesthesia completion, and mortality. The concentration of methemoglobin in arterial blood was measured every 6 hours.

Statistical data processing was performed using the IBM SPSS Statistics 26.0 software. The normality of data distribution was assessed using the Shapiro-Wilk test ($n \leq 50$). For non-parametric data, the median (Me), 25th and 75th percentiles were determined as Me (Q25;Q75). Comparison of quantitative data between the groups was performed using the Mann-Whitney test (independent groups). To compare categorical data between the groups, the Chi-square test was used. The significance level was taken as $p<0.05$.

Results

Table 3 presents a comparative assessment of dynamic changes over time in the acid-base state and blood gases between the groups.

Table 3 Comparative assessment of acid-base state and blood gas parameters in dynamics between the groups in the study

Parameters		Study group (n=23)	Comparison group (n=20)	p
Lactate, mmol/L (0.5;1.6)	After induction of anesthesia	1.3 (0.23;3.65)	1.2 (0.34;3.12)	0.512
	After anesthesia completion	3.9 (2.38;6.05)	5.4 (3.98;7.87)	0.034 *

pH (7.35;7.45)	After induction of anesthesia	7.44 (7.37;7.49)	7.41 (7.37;7.43)	0.631
	After anesthesia completion	7.38 (7.31;7.46)	7.34 (7.29;7.41)	0.544
Base deficit, mmol/L (0±2)	After induction of anesthesia	+ 5,1 (+4,1;+7,2)	+ 6.2 (+3.9;+8.1)	0.498
	After anesthesia completion	-2.5 (-5.1;-1.2)	-6.5 (-8.5;-2.2)	0.062
PaO_2/FiO_2	After induction of anesthesia	135 (122;151)	141 (121;165)	0.734
	After anesthesia completion	318 (267;399)	389 (237;412)	0.173
	24 hours after surgery	333 (266;383)	362 (213;412)	0.265
	48 hours after surgery	340 (278;426)	298 (192;365)	0.128
	72 hours after surgery	342 (261;398)	265 (235;356)	0.026*

Note: * - differences in parameter values are statistically significant between the groups ($p<0.05$) (Mann-Whitney). Data are presented as Me (Q25;Q75).

The results obtained indicated that the blood level of lactate at the stage after the anesthesia induction in all patients was within the reference values. However, after the anesthesia completion, in patients whose treatment included iNO-therapy, this parameter was statistically significantly lower by 1.4 times versus that in the comparison group. After the anesthesia completion, the patients receiving the standard therapy showed an increase in base deficit by 2.6 times compared with the study group ($p=0.062$).

After completion of anesthesia and at 24 hours after surgery, the oxygenation index (PaO_2/FiO_2) in patients who had received inhaled NO was lower by 1.2 times and 1.1 times, respectively, compared to patients on the standard therapy. It is noteworthy that at 48 and 72 hours after surgery, the level of the oxygenation index in the study group exceeded that in the comparison group by 1.1 times ($p=0.128$) and 1.3 times ($p=0.026$).

Table 4 shows the clinical criteria for the efficacy of the patient treatment in the study and comparison groups.

Table 4 Comparative assessment of the study groups with regard to the treatment efficacy criteria

Parameters		Study group (n=23)	Comparison group (n=20)	p
MLV duration, h		68 (24;132)	96 (43;215)	0.042*
VA-ECMO	Using VA-ECMO during surgery, n (%)	16 (69.5)	19 (95)	0.033*
	Using VA-ECMO after surgery, n (%)	10 (43.5)	14 (70)	0.474
	VA-ECMO duration of after surgery, hours	82 (65;121)	132 (79;145)	0.028*
Mortality, n (%)		8 (32)	8 (40)	0.577

Note: * - differences in parameter values are statistically significant between groups (p <0.05) (Mann-Whitney; Chi-square test). Quantitative data are presented as Me (Q25;Q75), those categorial as n, (%).

A comparative analysis of the obtained data showed that the median duration of MLV in patients of the study group was 68 (24;132) hours, which is 1.4 times less in patients of the comparison group (p=0.042). VA-ECMO during surgery was required in 69.5% of cases in the group of patients who received the iNO therapy versus 95% in the comparison group. VA-ECMO continued after surgery in 10 patients (43.5%) of the study group, in 14 patients (70%) of the comparison group. It is noteworthy that in patients whose treatment complex included iNO-therapy, the median duration of VA-ECMO after surgery was statistically significantly lower by 1.6 times (82 hours versus 132 hours). Mortality was 32% in the study group, 40% in the comparison group (p=0.577). The blood level of methemoglobin in the patients of the study group did not exceed that level in patients of the comparison group by more than 2%.

Discussion

Endogenous nitric oxide plays a decisive role in the regulation of vascular tone, being a powerful vasodilator produced by NO synthase

from L-arginine. Following reperfusion in lung transplantation, there is a decrease in endogenous NO level, leading to endothelial dysfunction. In this case, the use of exogenous NO is quite justified: as a result of a cascade of biochemical reactions, due to a decrease in the intracellular concentration of calcium ions, NO causes smooth muscle relaxation, a decrease in pulmonary hypertension and hypoxia, thereby improving the lung graft function [5].

To date, a number of studies have been conducted to evaluate the efficacy of iNO-therapy in pulmonary hypertension, in order to reduce and prevent ischemia-reperfusion lung transplant injury. However, they are controversial [12-19].

The results of the conducted studies indicated a positive effect of iNO-therapy on pulmonary hypertension in this type of surgery [12, 14, 15]. So, A. Ardehali et al. found that inhaled NO significantly improves gas exchange and reduces pressure in the pulmonary artery in patients with ischemia-reperfusion injury during LT [17]. With the withdrawal of iNO therapy, the authors observed an acute deterioration in gas exchange and an increase in pulmonary pressure, which were reflected in a decreased oxygenation index and a change in the central hemodynamic parameters. They concluded that the use of iNO has a positively effect on the gas exchange and pulmonary hypertension in patients with ischemia-reperfusion injury. This was also confirmed by previous studies [18, 19].

According to G. Thabut et al., inhaled nitric oxide and pentoxifylline before and during reperfusion significantly reduce the duration of mechanical ventilation compared to that in control groups 1 and 2 (2.1±2.4 days versus 7±9 days (p=0.02)/6±7 days (p=0.01)), lethality (4.3% versus 26% (p=0.04)/21% (p=0.07)). As follows from the authors' report, NO-therapy together with pentoxifylline reduces the likelihood of developing IRI [15]. Similar data was obtained by H. Date

et al. when using iNO-therapy [19]. According to C. Yerebakan e t al. nitric oxide inhalations prevent IRI and have a positive effect if it develops. According to the authors, nitric oxide is superior to other vasodilators in its selectivity to the pulmonary vasculature, without significant side effects on the systemic blood flow [20].

Other authors, on the contrary, have shown that the use of iNO-therapy does not prevent the development of primary graft dysfunction [17]. So, M. O Meade et al. conducted a randomized placebo-controlled trial to evaluate the effect of NO inhalations started at 10 minutes after the reperfusion on the treatment outcomes after lung transplantation. There were no statistically significant differences between in groups in the analyzed treatment efficacy criteria (oxygenation index, mechanical ventilation duration, time to extubation, hospital length of stay, mortality) [2].

In their cohort study, J. Fessler et al., found that a failure to wean from iNO-therapy in the postoperative period is an unfavorable prognostic sign: in this group of patients, the PGD incidence and mortality are higher [21].

We have found that iNO-therapy improves tissue perfusion and reduces hypoxia. It is known that uncorrected lactic acidosis after surgery is one of the factors affecting the patient survival [22, 23]. A faster increase in the oxygenation index with nitric oxide indicates the appropriateness of its use in patients undergoing lung transplantation. The study revealed statistically significant differences between the groups in PaO_2/FiO_2 values at 48 and 72 hours after surgery. Our data are consistent with the results of a number of studies [12, 14, 15, 17-19]. When studying the value of NO-therapy for the treatment efficacy, the following was established: a decrease in the need for using VA-ECMO during and after surgery (by 1.2 times and 1.4 times, respectively), a decrease in the

duration of VA-ECMO after surgery by 1.6 times, MLV duration decreased 1.9 times. In our opinion, this is due to the fact that the use of nitric oxide has a positive effect on hemodynamics and improves gas exchange. As such, there is no need for ECMO. It is known that important factors for predicting the outcome of patients after lung transplantation are the use of ECMO after surgery and the MLV duration for more than 3 days. The risk of death in a combination of these factors reaches 80% [23]. We should note that our study has shown no statistically significant differences between the groups in terms of mortality (32% versus 40%). And we should mention that our study is limited to a small sample of patients due to the fact that this group of diseases and the frequency of operations are rare.

The use of nitric oxide in the complex treatment according to our proposed method for lung transplantation had a positive effect on the course of intra - and early postoperative period, as evidenced by an improvement in blood gas parameters, a reduction in the frequency of veno-arterial extracorporeal membrane oxygenation use and its duration, and in the duration of mechanical ventilation. The data obtained suggest that the use of inhaled nitric oxide in the intraoperative and early postoperative period during lung transplantation reduces ischemia-reperfusion lung injury and thereby reduces the risk of developing a primary graft dysfunction (PGD). However, further studies are required to confirm this assumption.

Conclusions

1. The inhalation therapy with nitric oxide intraoperatively and in the early postoperative period has been established to improve tissue perfusion and reduce hypoxia, diminishing lactic acidosis.

2. An increase in the level of the oxygenation index by 1.1 times (p=0.128) and 1.3 times (p=0.026) was revealed at 48 and 72 hours after surgery, respectively, in patients with inhaled nitric oxide therapy, which indicates an improvement in ventilation perfusion ratio.

3. The use of inhaled nitric oxide therapy contributed to a decrease in the frequency of using extracorporeal membrane oxygenation during surgery by 1.2 times (p=0.033), the duration of mechanical lung ventilation by 1.4 times (p=0.042), and the duration of extracorporeal membrane oxygenation by 1.6 times (p=0.028).

4. It should be noted that in our study there were no statistically significant differences between the groups in terms of mortality (32% versus 40%).

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