ACTUAL ISSUES OF TRANSPLANTATION

https://doi.org/10.23873/2074-0506-2021-13-3-248-259

Comparative effectiveness of "liberal" and "restrictive" modes of intraoperative infusion-transfusion therapy in lung transplantation

A.M. Talyzin✉[1], S.V. Zhuravel[1], M.Sh. Khubutiya[1,2], E.A. Tarabrin[1], N.K. Kuznetsova[1]

[1]N.V. Sklifosovsky Research Institute for Emergency Medicine, 3 Bolshaya Sukharevskaya Sq., Moscow 129090 Russia;

[2]Department of Transplantology and Artificial Organs, A.I. Yevdokimov Moscow State University of Medicine and Dentistry, 1 Bldg. 20 Delegatskaya St., Moscow 127473 Russia

✉Corresponding author: Alexey M. Talyzin, Chief of the Department for Anesthesiology and Intensive Care № 3, N.V. Sklifosovsky Research Institute for Emergency Medicine, TalyzinAM@sklif.mos.ru

Abstract

***Background**. Recently, researchers have paid considerable attention to the strategy of intraoperative infusion-transfusion therapy in traumatic surgical interventions. The choice of a "restrictive" regimen during surgery in many studies has reduced the incidence and severity of intra- and postoperative complications.*

***Objective.** Comparison of the effectiveness of "liberal" and "restrictive" intraoperative infusion-transfusion therapy in lung transplantation.*

***Material and methods.** The study included 58 patients who underwent bilateral lung transplantation at N.V. Sklifosovsky Research Institute for Emergency Medicine in the period 2012-2019. The patients were divided into 2 groups: the comparison group included 31 patients, the total volume of intraoperative infusion-transfusion in whom was 14386.9 ±*

1310.0 ml (16.5 ml/kg/h). Group II consisted of 27 patients; their total volume of intraoperative infusion-transfusion during surgery was 10251.3 ± 740.1 ml (12.9 ml/kg/hour). The analysis we performed included the volume and composition of intraoperative infusion-transfusion therapy, the volume of blood loss, clinical and laboratory data, the duration of mechanical ventilation, the frequency of intraoperative use of veno-arterial extracorporeal membrane oxygenation and the duration of its use after surgery, mortality.

Results. *When using the "restrictive" fluid therapy for lung transplantation, we observed a decrease in the volume of intraoperative blood loss by 1.3 times, the volume of transfusion of blood components, including fresh frozen plasma by 37%, erythrocyte suspension by 3.1 times, and instrumental reinfusion of autoerythrocytes by 1.56 times. At the same time, we revealed a decrease by 2.7 times in the duration of the mechanical ventilation use, a decreased frequency of using veno-arterial extracorporeal membrane oxygenation during surgery by 1.3 times, and a decreased duration of using veno-arterial extracorporeal membrane oxygenation after surgery by 2.3 times. Mortality was 38.7% in group I, and 30.7 % in group II.*

Conclusion. *The “restrictive” approach to intraoperative infusion-transfusion therapy in lung transplantation seems a promising new trend requiring further study and gaining the experience.*

Keywords: lung transplantation, intraoperative infusion-transfusion therapy, restrictive fluid therapy, liberal fluid therapy

Conflict of interests Authors declare no conflict of interest

Financing The study was performed without external funding

For citation: Talyzin AM, Zhuravel SV, Khubutiya MSh, Tarabrin EA, Kuznetsova NK. Comparative effectiveness of "liberal" and "restrictive" modes of intraoperative

infusion-transfusion therapy in lung transplantation. *Transplantologiya. The Russian Journal of Transplantation.* 2021;13(3):248–259. (In Russ.). https://doi.org/10.23873/2074-0506-2021-13-3-248-259

BPsyst, systolic blood pressure
BPdiast, diastolic blood pressure
VA-ECMO, Veno-Arterial Extracorporeal Membrane Oxygenation
PCWP, pulmonary capillary wedge pressure
PAP, pulmonary artery pressure
MLV, mechanical lung ventilation
ITT, infusion-transfusion therapy
CBV, circulating blood volume
PGD, primary graft dysfunction
MAP, mean arterial pressure
CO, cardiac output
FFP, fresh frozen plasma
CI, cardiac index
LT, lung transplantation
COPD, chronic obstructive pulmonary disease
HR, heart rate
CVP, central venous pressure
ECMO, extracorporeal membrane oxygenation

Rationale

Bilateral lung transplantation (LT) is the only radical treatment option for patients with end-stage chronic lung diseases. This is a highly traumatic operation, usually accompanied by massive blood loss, unstable hemodynamics, and impaired pulmonary gas exchange, which in some cases requires intraoperative prosthetics of cardiorespiratory function, namely, the use of extracorporeal membrane oxygenation (ECMO) [1-5].

Despite significant advances in surgical techniques, improvements in immunosuppressive therapy regimens, and an optimization of donor conditioning; mortality in the early postoperative period after LT currently remains significant (3.6–12.5%) [2, 6, 7].

Recently, researchers have been paying great attention to approaches to intraoperative infusion and transfusion therapy (ITT) for surgical interventions, one of the most important components of anesthetic support. According to modern concepts, there are "liberal", "restrictive" and "goal-directed" (Goal Direct Therapy, GDT) ITT regimens [8, 9]. According to some authors, the volume of infusion with the "restrictive" strategy is from 2 mL/kg/h to 12 ml/kg/h; with the "liberal" approach it reaches 30 mL/kg/h [10]. A number of studies have shown that the "liberal" version of ITT leads to an impairment of the vascular-endothelial barrier, the development of difficult-to-treat edematous syndrome, multiple organ failure, severe coagulation disorders, and, accordingly, an increased length of stay in intensive care unit, and an increase in postoperative mortality [11-13]. On the contrary, the choice of a "restrictive" (limited) ITT strategy during operations in major abdominal and thoracic surgery in many studies reduced the incidence and severity of intra- and postoperative complications [14-18]. However, with this approach, there is a risk of developing uncorrected hypovolemia, which leads to organ hypoperfusion. A "targeted" (GDT) ITT strategy based on transesophageal Doppler monitoring of cardiac output (CO) has a limited application in general practice [9].

We should note that there are insufficient studies devoted to the peculiarities of intraoperative ITT in lung transplantation. According to a few publications, an increase in the intraoperative ITT volume increases the risk of primary graft dysfunction [1, 19, 20]. It is known that the recipients who have undergone transfusion of significant amounts of packed red blood cells have a high risk of developing a primary pulmonary graft dysfunction, which, in turn, leads to an increased risk of fatal outcome [2]. The lack of convincing evidence for the optimal tactics of intraoperative ITT and its structure in lung transplantation prompted us to conduct this study.

The study objective was to compare the efficacy of "liberal" and "restrictive" intraoperative ITT regimens in LT.

Material and methods

The material of the retrospective study was the data from medical records of in-hospital patients. We selected the case histories of 58 patients who underwent bilateral lung transplantation at N.V.Sklifosovsky Research Institute for Emergency Medicine in the period from 2012—2019. There were 24 women (41.4%) and 34 men (58.6%). The mean age of patients was 35.8 [27; 44] years.

The patient distribution by nosological groups before surgery, according to the United Network for Organ Sharing (UNOS) principles, was as follows: obstructive diseases (chronic obstructive pulmonary disease [COPD]/emphysema, bronchiectasis, sarcoidosis (with average pulmonary artery pressure < 30 mm Hg), lymphangioleiomyomatosis, obliterating bronchiolitis) in 18 patients (31%), vascular diseases (idiopathic pulmonary hypertension, Eisenmenger syndrome) in 3 (5.2%), cystic fibrosis in 24 (41.4%), immunodeficiency syndromes, restrictive diseases (idiopathic pulmonary fibrosis, sarcoidosis with average pulmonary artery pressure ≥ 30 mm Hg) in 13 (22.4%). All patients underwent the procedure according to the protocol of preoperative examination of a LT recipient. Anesthesia was performed according to the standard protocol. Intraoperative ITT included the introduction of crystalloid and colloid solutions (hydroxyethyl starch 6%) as well as the transfusion of blood components. The erythrocyte suspension was transfused in a decreased hemoglobin level below 80 g/L. In addition to allogeneic blood transfusion, autoerythrocyte transfusion was performed. When coagulopathy developed, fresh frozen plasma (FFP) was transfused. In a decreased mean arterial pressure (MAP) < 60 mm Hg despite the ongoing ITT, the administration of vasopressors and inotropes (norepinephrine, dobutamine, dopamine) was initiated. The central veno-arterial ECMO (VA-ECMO) was included in the treatment complex in patients with uncontrolled hypoxemia, unstable hemodynamics, and increased lactic acidosis.

According to the data obtained at reviewing the inpatient medical data records of 58 patients, and with regard of the intraoperative ITT amount and the volume of colloidal blood substitutes used in it, two groups were distinguished. Group I included 31 patients whose total ITT volume was 14,386.9±1,310.0 mL (16.5 mL/kg/hr), and the intraoperative volume of colloids was more than 500 mL (Table 1); group II consisted of 27 patients whose total volume of ITT during surgery was more "restrictive" 10,251.3±740.1 mL (12.9 mL/kg/h), and the volume of colloid solutions did not exceed 500 mL.

Table 1. General characteristics of study groups

Parameters	Group I	Group II	P
Number of patients, n	31	27	
Total volume of ITT, mL (mL/kg/hour)	14386.9±1310.0 (16.5)	10251.3±740.1 (12.9)*	0.005
The volume of colloid solutions, mL	> 500	< 500	
Age, years	33.59±9.94	37.29±12.13	0.634
Men, n (%)	15 (48.4)	18 (66.6)	0.375
Women, n (%)	16 (51.6)	9 (33.4)	0.174
Restrictive diseases, n (%)	6 (19.3)	7 (25.9)	0.538

Note: * - asterisk denotes statistically significant differences in parameter values between the groups (p <0.05).

The groups were comparable in age, the number of patients with restrictive diseases (6 pts in group I; 7 pts in group II), which were associated with the highest risk of an unfavorable outcome, the total ischemia time and graft cold ischemia time.

To solve the tasks set, the following parameters were analyzed: the ITT volume and composition, the volume of blood loss (gravimetric method and results of red blood cell reinfusion), the surgery duration, and the arterial blood gases, the acid-base state of blood after the induction of anesthesia and the completion of anesthesia. The oxygenation index (PAO_2/FiO_2) was evaluated additionally at 24, 48, and 72 hours after surgery to diagnose a primary graft dysfunction. The endpoints of the study include also the duration of mechanical lung ventilation (MLV), the frequency of intraoperative VA-ECMO use and the duration of VA-ECMO use after surgery, and mortality.

Statistical data processing was performed using Statistica 13.3 software from StatSoft®. The normality of the data distribution was evaluated using the Shapiro-Wilk test at $n \leq 50$. For a normal distribution, the arithmetic mean (M) and standard deviation (SD) were determined. For nonparametric data, the median (Me), the 25th and 75th percentiles, and the interquartile range (IQR) were determined. Quantitative data were compared between the groups using Student's t-test (M±Q) (normal distribution) and Mann-Whitney test (M-W) (the distribution differs from the normal one). The Pearson's $\chi 2$ test was used to compare qualitative data between groups. The difference significance level was $p<0.05$.

Results and discussion

Analysis of the obtained results showed that the duration of surgical intervention did not significantly differ between the two groups: 866.6±32.5 minutes in group I, 764.8±34.2 minutes in group II.

Table 2 shows a comparative assessment of the volume and composition of infusion and transfusion media administered during surgery in patients of both groups.

Table 2. Comparative characteristics of the volume and components of infusion-transfusion therapy in the study groups

Parameters	Group I (n=31)	Group II (n=27)	P
Total volume of infusion-transfusion therapy, mL	14 386.9±1350.2	10 251.3±740.1*	0.005
Blood loss volume, mL	3745.2±638.0	2805.6±537.7	0.134
The volume of crystalloid solutions, mL	8707.0±1055.1	7551.6±538.8	0.645
The volume of colloid solutions, mL	2680.2±313.2	478.2±162.3*	0.018
Fresh frozen plasma, mL	1982.1±335.9	1245.1±245.4	0.394
Erythrocyte suspension, mL	2018.1±265.3	647.6±194.6	0.075
Instrumental reinfusion of autoerythrocytes, mL	726.8±166.2	464.7±162.8	0.132
Thromboconcentrate, n (%)	8 (25.8%)	1 (3.7%)*	0.020
Norepinephrine, n (%)	31 (100)	27 (100)	0.924
Dobutamine, n (%)	29 (93.5)	24 (88.8)	0.528
Dopamine, n (%)	9 (29.0)	7 (25.9)	0.792

Note: * - the asterisk denotes statistically significant differences in parameter values between the groups ($p < 0.05$).

Data are presented as M ± SD

The total volume of intraoperative ITT in patients of group I was 14,386.9±1,350.2 mL (16.5 mL/kg/h), which was 1.4 times higher than in group II 10,251.3±740.1 mL (12.9 mL/kg/h), the difference was statistically significant. When analyzing the intraoperative ITT composition, we noted that the volume of crystalloid solutions did not differ statistically significantly between the groups: 8707.0±1055.1 mL in group I versus 7551.6±538.8 mL in the comparison group. The volume of colloid solutions in patients of group II was 5.6 times lower ($p<0.05$) compared to the patients of group I (478.2±162.3 mL vs. 2680.2±313.2 mL). The results obtained during the study showed that colloid solutions were administered to patients of group I to stop acute hypovolemia caused by bleeding, while in group II they began to administer crystalloid solutions, and if they were not effective enough, they used colloids.

The data obtained indicated that the volume of intraoperative blood loss in group I patients was 3745.2±638.0 mL, which was 1.3 times higher than in group II. Accordingly, the volume of transfused blood components in group I was higher. Thus, the volume of FFP in group I was 1982.1±335.9 mL versus 1245.1±245.4 ml in group II, the erythrocyte suspension volume was 2018.1±265.3 mL in group I versus 647.6±194.6 mL in group II; the instrumental reinfusion of autoerythrocytes was 726.8±166.2 mL in patients of group I, and 464.7±162.8 mL in group II. Thromboconcentrate transfusion was performed in 8 patients in group I, and one patient in group II. All patients required intraoperative administration of vasopressor/inotropic drugs (norepinephrine, dobutamine, dopamine). In 100% of cases in both groups, norepinephrine was used, while the number of patients treated with dobutamine and dopamine in group I was higher than in group II: 29 (93.5%) versus 24 (88.8%) patients and 9 (29%) versus 7 (25.9%) patients, respectively.

The results of a comparative assessment of the acid-base state, blood gas composition after the induction of anesthesia and after the completion of anesthesia are presented in Table 3.

Table 3. Changes in laboratory parameters over time in patients of the study groups

Parameters	Stages	Group I (n=31)	Group II (n=27)	P
Lactate, mmol/L (0.5-1.6)	1	1.2 (0.3–3.6)	1.32 (0.1–2.9)	0.645
	2	5.7 (2.7–9.0)	3.7 (2.1–4.7)*	0.021
pH (7.35-7.45)	1	7.46 (7.41–7.51)	7.47 (7.42–7.52)	0.938
	2	7.34 (7.31–7.47)	7.37 (7.29–7.40)	0.534
BE, mmol/L (0 ± 2)	1	+6 (+4.2–+8.0)	+7 (+4.3–+9.3)	0.395

	2	–5.5 (–7.5—2)	–3 (–5.6– –1.9)	0.083
Glucose, mmol/L	1	5.4 (3.3–6.7)	5.6 (3.5–7.6)	0.828
	2	12.3 (7.85–15.2)	10.9 (8.70–16.0)	0.139
P_aO_2/FiO_2	1	139 (125.1–156.3)	145 (125.3–165.2)	0.274
	2	351.0 (290.0–521.5)	277.0 (228.0–348.0)	0.184
	3	320.0 (275.5–498.0)	339.0 (263.0–382.5)	0.629
	4	340.0 (254.0–700.0)	360.0 (280.0–429.0)	0.734
	5	275.0 (245.0–446.0)	356.0 (256.0–400.0)*	0.018

Notes. * - the asterisk denotes statistically significant differences in parameter values between the groups ($p < 0.05$).

Stages of the study. 1: after anesthesia induction; 2: after anesthesia completion; 3: 24 hours after surgery; 4: 48 hours after surgery; 5: 72 hours after surgery.

Data are presented as median (interquartile range)

A dynamic study of the blood lactate revealed an increase in its level after anesthesia completion in all patients, but this parameter was statistically significantly increased (by 1.5 times) in group I patients compared to group II. A similar trend was observed with base deficit; by the end of surgery this parameter in group I was 1.4 times higher than in group II.

Initially, normoglycemia was detected in both groups; after anesthesia was completed, all patients showed an increase in blood glucose (12.3 mmol/L in group I versus 10.9 mmol/L in group II).

The dynamic study of the oxygenation index (PaO_2/FiO_2) showed the growth after the completion of anesthesia (stage 2) in patients of both groups, but in group I its level was 1.3 times higher compared to the group of patients who underwent a "restrictive" ITT. Noteworthy is the statistically significant increase in PaO_2/FiO_2 after 72 hours in group II compared to group I (by 1.3 times).

Table 4 shows the comparison of results between the groups according to the criteria of treatment efficacy.

Table 4. Comparison of the treatment results between the study groups according to the treatment efficacy criteria

<table>
<tr><th colspan="2">Parameters</th><th>Group I (n=31)</th><th>Group II (n=27)</th><th>P</th></tr>
<tr><td colspan="2">MLV duration, h,</td><td>148.0 (18.0–321.0)</td><td>54.8 (24.0–74.0)*</td><td>0.004</td></tr>
<tr><td rowspan="2">VA-ECMO</td><td>VA-ECMO use during surgery, n (%)</td><td>31 (100)</td><td>20 (74)*</td><td>0.003</td></tr>
<tr><td>VA-ECMO duration after surgery, h</td><td>170.7 (18–321)</td><td>72.2 (24–116)*</td><td>0.032</td></tr>
<tr><td colspan="2">Mortality, n (%)</td><td>12 (38.7)</td><td>8 (30.7)</td><td>0.468</td></tr>
</table>

Notes. * - the asterisk denotes statistically significant differences in parameter values between the groups (p <0.05);

Data are presented as median (interquartile range)

We revealed that the mechanical ventilation duration in group I patients was reduced was significantly higher than in group II (by 2.7 times; 148.0 hours vs. 54.8 hours). VA-ECMO was used during surgery in 100% of cases in group I, in 74% of cases (20 patients) in group II (p<0.05); 7 patients did not require the VA-ECMO use. We should note that the use of VA-ECMO was intraoperatively discontinued in 7 patients (22.6%) of group I versus 8 (29.6%) patients of group II. Meanwhile, in patients in whom VA-ECMO was continued after surgery, its duration was 170.7 (18;321) hours in group I, which was 2.35 times higher (p<0.05) than in patients of group II. The mortality rate was 38.7% in group I, and 30.7% in group II.

Discussion

Currently, it is known that the incidence of postoperative complications and the LT outcome largely depend on such components of anesthesia and resuscitation support as effective intraoperative analgesia, ITT, and the amount of the blood loss and the volume of transfused blood components [21].

The development of primary pulmonary graft dysfunction (PGD) due to ischemic-reperfusion injury in the first hours after arterial reperfusion is one of the most severe complications in LT and causes more than 30% of postoperative deaths. Lung damage begins as early as in the donor during the dying process due to pronounced stress endocrine-metabolic reactions and systemic inflammation and reaches its peak after intraoperative organ reperfusion [22]. A decrease in the clearance of alveolar fluid due to an impaired lymphatic drainage aggravates this process. Probably, in this regard, the transplanted lungs are particularly sensitive to the infusion of a large fluid volume [23, 24]. According to modern concepts, hyperinfusion is also one of the most frequent factors damaging the endothelial glycocalyx, leading to acute graft damage [9]. The infusion of an increased fluid volume can contribute to the PGD development due to the increase in cardiac filling, which, in turn, increases the pulmonary blood flow and exacerbates ischemic-reperfusion damage. A number of authors have shown that the volume and composition of intraoperative ITT significantly affect the PGD severity degree. Thus, M.A. Geube et al. found that each liter of infusion during surgery increased the risk of developing grade 3 PGD by 22%, but the authors did not find a link between the use of various components of infusion therapy (colloids, crystalloids) and the PGD development [20]. Meantime, in their study D.R. McIlroy et al. demonstrated an independent inverse relationship between the volume of colloid solutions and the development of grade 2 PGD 12 hours after transplantation, and an increase in the treatment duration in the intensive care unit [19]. The authors explain this by the increased capillary permeability that occurs during PGD, as a result of which relatively large colloidal solution molecules move into the extravascular lung space. The complete absence of lymphatic drainage in the transplanted lung can further slow down the elimination of oncotically active molecules from the lung [25-27]. A number of authors, based on the results of their studies, made a similar conclusion that the number of intraoperatively administered solutions is important for preventing the development of complications and the successful treatment outcome [28, 29].

According to literature reports, one of the risk factors leading to the development of grade 2-3 primary graft dysfunction (PGD) and the death is a large amount of blood loss during surgery and, accordingly, the volume of blood transfusion [2, 30-32]. Y. Liu et al. found a relationship between the development of grade 3 PGD and the volume of FFP. Weber et al. proved that transfusion of blood components leads to an increase in mortality after LT [33-37].

At the same time, there is no convincing evidence in favor of applying a restrictive ITT strategy in LT. There are no high-quality randomized clinical trials to study the benefits of using a particular regimen of perioperative ITT in LT. It is known that the use of a "restrictive" ITT strategy during surgical interventions can lead to hypovolemia, reduced cardiac output, vasoconstriction, ischemia of organs and tissues, including the kidneys, intestines, pancreas, and surgical anastomoses. Without the replenishment of the circulating blood volume (CBV) the stroke volume continues decreasing, and the organ ischemia deteriorates [9]. A number of studies comparing the efficacy of "liberal" and "restrictive" ITT regimens have been conducted for extensive surgical interventions in abdominal surgery. Meanwhile, the advantages of using restrictive tactics were not obvious. Thus, when using the "restrictive " ITT regimen in the intra- and early postoperative periods, an increased risk of developing postoperative renal dysfunction was observed, while no differences in patient survival were found [38, 39]. We should also note the inconsistency in the design of conducted studies. That was caused by heterogeneity of ITT volumes, which the authors took for "restrictive" and "liberal" regimens, errors in methodological standardization, and the choice of endpoints. It seems that research in this direction should be continued.

The literature data analysis has shown that currently there is not enough material to study the advantages of one or another approach to performing perioperative ITT in LT. Based on individual scientific publications, it is difficult to shape a uniform idea of the correct ITT strategy, whereas this is of particular importance for LT.

Evaluation of the obtained results showed statistically significant differences in the volume of infusion therapy during the entire surgical intervention (14,386.9±1,350.2 mL [16.5 mL/kg/h] in group I versus 10,251.3±740.1 mL [12.9 mL/kg/h] in group II) due to an increase in the volume of colloid solutions ($p<0.5$) by 5.6 times. The volume of crystalloid solutions did not differ significantly between the groups.

A decrease in the volume of intraoperative blood loss by 1.3 times was found in the patients who underwent "restrictive" ITT compared to the patients in the comparison group. The result was a marked reduction in the transfusion of blood components due to decreased ITT volume: the transfused FFP volume decreased by 37% (1245.1±245.4 mL in group II vs. 1982.1±335.9 mL in group I); the erythrocyte suspension volume decreased 3.1-fold (647.6±194.6 mL in group II vs. 2018.1±of 265.3 mL in group I), instrumental reinfusion of autoerythrocytes decreased by 1.56 times (464.7±162.8 mL in group II vs. 726.8±166.2 mL in group I), the platelet concentrate was used in 8 patients of group I, and in one case of group II.

Lactic acidosis, which level was higher after anesthesia completion in patients of group I, indicated hypoperfusion and tissue hypoxia. According to literature reports, one of the intraoperative factors affecting the patient survival after lung transplantation is uncorrected lactic acidosis after surgery [2]. At anesthesia completion, the patients in both groups, more pronounced in group I, showed an increase in the initially normal blood glucose level, apparently as a response to surgical stress and blood loss [17, 18]. Hyperglycemia is referred to a mandatory manifestation of the stress response, and the degree of increase in blood glucose levels usually correlates with the severity of the surgical injury. It is also known that hyperglycemia can occur as a result of disproportionate infusion therapy (hyperinfusion), which leads to rapid destruction of glycocalyx and the development of "capillary leakage" syndrome [9]. The oxygenation index (PaO_2/FiO_2) was studied in dynamics. According to the PGD classification developed by the International Society for Heart and Lung Transplantation, a change in the level of PaO_2/FiO_2 corresponds to the severity of ischemic reperfusion injury [2, 20]. The increase in PaO_2/FiO_2 was observed after the anesthesia completion (stage 2) in patients of both groups. Meanwhile, its level was 1.3 times higher in group I than in group II patients. Apparently, this is due to the fact that all patients of group I required the use of VA-ECMO during surgery, 25 of whom required it after surgery, while in group II, 7 patients did not use VA-ECMO during surgery, in 8 cases they finished using VA-ECMO immediately after the end of anesthesia. A statistically significant 1.3-fold increase in PaO_2/FiO_2 was found after 72 hours in the patients who underwent "restrictive" ITT compared to the comparison group.

When studying the effect of different ITT regimens in LT on the treatment efficacy, we noted a decrease in the mechanical ventilation duration by 2.7 times with a "restrictive" ITT strategy, as well as a reduction by 1.3 times in the frequency of VA-ECMO use during surgery, and by 2.3 times in the VA-ECMO duration after surgery, and a decreased mortality being 30.7% in group II versus 38.7% in group I patients.

According to literature, the most important factors for predicting the outcome of patients after LT are the use of ECMO after surgery and the duration of mechanical ventilation for more than 3 days. The risk of death with a combination of these factors reaches 80%. Performing mechanical ventilation in the postoperative period for more than 3 days contributes to the development of pneumonia and sepsis, increasing the risk of death [2, 38]. When using ECMO during surgery, a higher incidence of intraoperative bleeding was revealed.

The obtained data showed that the use of the "restrictive" regimen of infusion-transfusion therapy in lung transplantation has a positive effect on clinical and biochemical parameters, arterial blood gases, acid-base state, reduces the amount of blood loss and the volume of blood components transfused, leads to a decreased duration of mechanical lung ventilation, the frequency of veno-arterial extracorporeal membrane oxygenation during surgery, and the duration of veno-arterial extracorporeal membrane oxygenation after surgery. Thus, the use of the "restrictive" strategy to infusion-transfusion therapy reduces the likelihood of factors leading to the development of complications, which generally improves the disease prognosis. This approach of intraoperative infusions for bilateral transplantation seems promising, but it requires further study and accumulation of experience. The development of central hemodynamics monitoring technologies and their availability will make it possible to personalize infusion and transfusion therapy in lung transplantation and switch to "goal-directed" (GDT) tactics, which will help to increase the efficacy and safety of this component of perioperative intensive care and improve treatment results in general.

Conclusions

1. The use of the "restrictive" strategy of intraoperative infusion and transfusion therapy in lung transplantation reduces the volume of intraoperative blood loss by 1.3 times and reduces the volume of transfused blood components: fresh frozen plasma by 37%; red blood cell suspension by 3.1 times, instrumental reinfusion of autoerythrocytes by 1.56 times.

2. The "restrictive" strategy of intraoperative infusion-transfusion therapy has a positive effect on tissue perfusion, reducing lactic acidosis; it leads to the normalization of the oxygenation index in the postoperative period, which is expressed in its statistically significant increase by 1.3 times after 72 hours compared to that in group I.

3. The use of the "restrictive" strategy of intraoperative infusion and transfusion therapy in lung transplantation reduces the mechanical lung ventilation duration by 2.7 times, reduces the frequency of veno-arterial extracorporeal membrane oxygenation during surgery by 1.3 times, reduces the duration of veno-arterial extracorporeal membrane oxygenation after surgery by 2.3 times, and reduces the mortality rate by 8%.

References

1. Tomasi R, Betz D, Schlager S, Kammerer T, Hoechter DJ, Weig T, et al. Intraoperative anesthetic management of lung transplantation: center-specific practices and geographic and centers size differences. *J Cardiothorac Vasc Anesth.* 2018;32(1):62–69. PMID: 29174123 https://doi.org/10.1053/j.jvca.2017.05.025

2. Kurilova OA, Zhuravel SV, Romanov AA, Marinin PN, Tsurova DKh, Kallagov TE, et al. Experience with application of extracorporeal membrane oxygenation in double lung transplantation. *Russian Journal*

of Transplantology and Artificial Organs. 2014;16(2):66–74. (In Russ.). https://doi.org/10.15825/1995-1191-2014-2-66-74

3. Miranda A, Zink R, McSweeney M. Anesthesia for Lung Transplantation. *Semin Cardiothorac Vasc Anesth*. 2005;9(3):205–212. PMID: 16151553 https://doi.org/10.1177/108925320500900303

4. Della Rocca G, Brondani A, Costa MG. Intraoperative hemodynamic monitoring during organ transplantation: what is new? *Curr Opin Organ Transplant*. 2009;14(3):291–296. PMID: 19448537 https://doi.org/10.1097/mot.0b013e32832d927d

5. Weiss ES, Allen JG, Meguid RA, Patel ND, Merlo CA, Orens JB, et al. The impact of center volume on survival in lung transplantation: an analysis of more than 10,000 cases. *Ann Thorac Surg*. 2009;88(4):1062–1070. PMID: 19766782 https://doi.org/10.1016/j.athoracsur.2009.06.005

6. Christie JD, Carby M, Bag R, Corris P, Hertz M, Weill D. Report of the ISHLT working group on primary lung graft dysfunction: part II definition. *J Heart Lung Transplant*. 2005;24(10):1454–1459. PMID: 16210116 https://doi.org/10.1016/j.healun.2004.11.049

7. Prekker ME, Nath DS, Walker AR, Johnson AC, Hertz MI, Herrington CS, et al. Validation of the proposed International Society for Heart and Lung Transplantation grading system for primary graft dysfunction after lung transplantation. *J Heart Lung Transplant*. 2006;25(4):371–378. PMID: 16563963 https://doi.org/10.1016/j.healun.2005.11.436

8. Kravets OV, Klygunenko OM. Optimal strategy of perioperative infusion: pros and cons. *Emergency Medicine = Medicina neotložnyh sostoânij*. 2019;(3):14–20. (In Russ.). https://doi.org/10.22141/2224-0586.3.98.2019.165472

9. Zabolotskikh IB, Protsenko DN. (ed.) *Intensivnaya terapiya: natsional'noe rukovodstvo:* in 2 vol. V. 1. 2nd ed., revised and enlarged. Moscow: GEOTAR-Media Publ.; 2020. (In Russ.).

10. Giorgio D. Rocca, Luigi V, Gabriella T, Cristian D, Federico B, Livia P. Liberal or restricted fluid administration: are we ready for a proposal of a restricted intraoperative approach? *BMC Anesthesiol.* 2014;14:62. PMID: 25104915 https://doi/org/10.1186/1471-2253-14-62 eCollection 2014.

11. Mythen MG, Swart M, Acheson N, Crawford R, Jones K, Kuper M, et al. Perioperative fluid management: consensus statement from the enhanced recovery partnership. *Perioper Med (Lond).* 2012;1:2. PMID: 24764518 https://doi.org/10.1186/2047-0525-1-2

12. Watt DG, McSorley ST, Horgan PG, McMillan DC. Enhanced recovery after surgery: which components, if any, impact on the systemic inflammatory response following colorectal surgery? A systematic review. *Medicine (Baltimore).* 2015;94(36):e1286. PMID: 26356689 https://doi.org/10.1097/MD.0000000000001286

13. Minto G, Mythen MG. Perio-perative fluid management: science, art or random chaos? *Br J Anaesth.* 2015;114(5):717–721. PMID: 25794505 https://doi.org/10.1093/bja/aev067

14. Brandstrup B, Tønnesen H, Beier-Holgersen R, Hjortsø E, Ørding H, Lindorff-Larsen K, et al. Effects of intravenous fluid restriction on postoperative complications: comparison of two perioperative fluid regimens:a randomized assessor-blinded multicenter trial. *Ann Surg.* 2003;238(5):641–648. PMID: 14578723 https://doi.org/10.1097/01.sla.0000094387.50865.23

15. Nisanevich V, Felsenstein I, Almogy G, Weissman C, Einav S, Matot I. Effect of intraoperative fluid management on outcome after

intraabdominal surgery. *Anesthesiology.* 2005;103(1):25–32. PMID: 15983453 https://doi.org/10.1097/00000542-200507000-00008

16. Dzyadzko AM, Katin ML, Chugunova OA, Minov AF, Oganova EG, Santotskiy EO, et al. The effect of using the algorithm of restrictive intraoperative fluid therapy, early immune enteral nutrition, and early patient mobilization on orthotopic liver transplantation outcomes. *Transplantologiya. The Russian Journal of Transplantation.* 2016;(3):10–20. (In Russ.).

17. Tipisev DA, Gorobets ES, Gruzdev VE, Anisimov MA, Borovkova NB, Kochkovaya EO. Whether postoperative mechanical ventilation is always mandatory for patients suffered of intraoperative massive hemorrhage in elective surgery: arguments and cases of single hospital. *Intensive Care Herald.* 2016;4:52–58. (In Russ.).

18. Mierzweska-Schmidt M. Intraoperative fluid management in children – a comparison of three fluid regimes. *Anaesthesiol Intensive Ther.* 2015;47(2):125–130. PMID: 25940329 https://doi.org/10.5603/AIT.2015.0012

19. McIlroy DR, Pilcher DV, Snell GI. Does anaesthetic management affect early outcomes after lung transplant? An exploratory analysis. *Br J Anaesth.* 2009;102(4):506–514. PMID: 19224927 https://doi.org/10.1093/bja/aep008

20. Geube MA, Perez-Protto SE, McGrath TL, Yang D, Sessler DI, Budev MM, et al. Increased intraoperative fluid administration is associated with severe primary graft dysfunction after lung transplantation. *Anesth Analg.* 2016;122(4):1081–1088. PMID: 26991618 https://doi.org/10.1213/ANE.0000000000001163

21. Castillo M. Anesthetic management for lung transplantation. *Curr Opin Anaesthesiol.* 2011;24(1):32–36. PMID: 21084981 https://doi.org/10.1097/aco.0b013e328341881b

22. Lee JC, Christie JD, Keshavjee S. Primary graft dysfunction: definition, risk factors, short- and long-term outcomes. *Semin Respir Crit Care Med*. 2010;31(2):161–171. PMID: 20354929 https://doi.org/10.1055/s-0030-1249111

23. Sugita M, Ferraro P, Dagenais A, Clermont ME, Barbry P, Michel RP, et al. Alveolar liquid clearance and sodium channel expression are decreased in transplanted canine lungs. *Am J Respir Crit Care Med*. 2003;167(10):1440–1450. PMID: 12738601 https://doi.org/10.1164/rccm.200204-312OC

24. Peltracco P, Falasco G, Barbieri S, Milevoj M, Serra E, Ori C. Anesthetic considerations for nontransplant procedures in lung transplant patients. *J Clin Anesth*. 2011;23(6):508–516. PMID: 21911200 https://doi.org/10.1016/j.jclinane.2011.05.002

25. Shargall Y, Guenther G, Ahya VN, Ardehali A, Singhal A, Keshavjee S. Report of the ISHLT working group on primary lung graft dysfunction part VI: treatment. *J Heart Lung Transplant*. 2005;24(10):1489–1500. PMID: 16210120 https://doi.org/10.1016/j.healun.2005.03.011

26. Arif SK, Verheij J, Groeneveld AB, Raijmakers PG. Hypoproteinemia as a marker of acute respiratory distress syndrome in critically ill patients with pulmonary edema. *Intensive Care Med*. 2002;28(3):310–317. PMID: 11904661 https://doi.org/10.1007/s00134-002-1220-y

27. Groeneveld AB. Radionuclide assessment of pulmonary microvascular permeability. *Eur J Nucl Med*. 1997;24(4):449–461. PMID: 9096099 https://doi.org/10.1007/BF00881821

28. Sankar NM, Ramani SS, Vaidyanathan K, Cherian KM. Anaesthetic and perioperative management of lung transplantation.

Indian J Anaesth. 2017;61(2):173–175. PMID: 28250489 https://doi.org/10.4103/ija.IJA_512_16

29. Navarro LH, Bloomstone JA, Auler JO Jr, Cannesson M, Rocca GD, Gan TJ, et al. Perioperative fluid thera-py: a statement from the international Fluid Optimization Group. *Perioper Med (Lond).* 2015;4:3. PMID: 25897397 https://doi.org/10.1186/s13741-015-0014-z eCollection 2015.

30. Diamond JM, Lee JC, Kawut SM, Shah RJ, Localio AR, Bellamy SL, et al. Clinical risk factors for primary graft dysfunction after lung transplantation. *Am J Respir Crit Care Med.* 2013;187(5):527–534. PMID: 23306540 https://doi.org/10.1164/rccm.201210-1865OC

31. Liu Y, Liu Y, Su L, Jiang SJ. Recipient-related clinical risk factors for primary graft dysfunction after lung transplantation: a systematic review and meta-analysis. *PLoS One.* 2014;9(3):e92773. PMID: 24658073 https://doi.org/10.1371/journal.pone.0092773 eCollection 2014.

32. DeLima NF, Binns OA, Buchanan SA, Mauney MC, Cope JT, Shockey KS, et al. Euro-Collins solution exacerbates lung injury in the setting of high-flow reperfusion. *J Thorac Cardiovasc Surg.* 1996;112(1):111–116. PMID: 8691854 https://doi.org/10.1016/s0022-5223(96)70184-8

33. Oechslin P, Zalunardo MP, Inci I, Schlaepfer M, Grande B. Established and potential predictors of blood loss during lung transplant surgery. *J Thorac Dis.* 2018;10(6):3845–3848. PMID: 30069385 https://doi.org/10.21037/jtd.2018.05.165

34. Lodewyks C, Heinrichs J, Grocott HP, Karkouti K, Romund G, Arora RC, et al. Point-of-care viscoelastic hemostatic testing in cardiac surgery patients: A systematic review and meta-analysis. *Can J Anaesth.* 2018;65(12):1333–1347. PMID: 30194674 https://doi.org/10.1007/s12630-018-1217-9

35. Smith I, Pearse BL, Faulke DJ, Naidoo R, Nicotra L, Hopkins P, et al. Targeted bleeding management reduces the requirements for blood component thera-py in lung transplant recipients. *J Cardiothorac Vasc Anesth.* 2017;31(2):426–433. PMID: 27692703 https://doi.org/10.1053/j.jvca.2016.06.027

36. Bhaskar B, Zeigenfuss M, Choudhary J, Fraser JF. Use of recombinant activated Factor VII for refractory after lung transplant bleeding as an effective strategy to restrict blood transfusion and associated complications. *Transfusion.* 2013;53(4):798–804. PMID: 22845023 https://doi.org/10.1111/j.1537-2995.2012.03801.x

37. Barac YD, Klapper J, Pollack A, Poisson J, Welsby I, Hartwig MG, et al. Anticoagulation strategies in the periope-rative period for lung transplant. *Ann Thorac Surg.* 2020;110(1):e23–e25. PMID: 31981503 https://doi.org/10.1016/j.athoracsur.2019.11.056

38. Rhodes A, Cecconi M, Hamilton M, Poloniecki J, Woods J, Boyd O, et al. Goal-directed therapy in high-risk surgical patients: A 15-year follow-up study. *Intensive Care Med.* 2010;36(8):1327–1332. PMID: 20376431 https://doi.org/10.1007/s00134-010-1869-6

39. Pestaña D, Espinosa E, Eden A, Nájera D, Collar L, Aldecoa C, et al. Perioperative goal-directed hemodynamic optimization using noninvasive cardiac output monitoring in major abdominal surgery: A prospective, randomized, multicenter, pragmatic trial: POEMAS Study (PeriOperative goal-directed thErapy in Major Abdominal Surgery). *Anesth Analg.* 2014;119(3):579–587. PMID: 25010820 https://doi.org/10.1213/ANE.0000000000000295

40. Martin AK, Yalamuri SM, Wilkey BJ, Kolarczyk L, Fritz AV, Jayaraman A, et al. The Impact of Anesthetic Management on Perioperative Outcomes in Lung Transplantation. *J Cardiothorac Vasc*

Anesth. 2020;34(6):1669–1680. PMID: 31623969 https://doi.org/10.1053/j.jvca.2019.08.037

Information about the authors

Alexey M. Talyzin, Chief of the Department for Anesthesiology and Intensive Care № 3, N.V. Sklifosovsky Research Institute of Emergency Medicine, https://orcid.org/0000-0003-0830-2313

40%, literature review, data collection and processing of results, analysis of the data obtained, writing a draft manuscript

Sergey V. Zhuravel, Dr. Sci. (Med.), Head of the Scientific Anesthesiology Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-9992-9260

20%, development of the study design, analysis of the data obtained, the article text revision and approval

Mogeli Sh. Khubutiya, Academician of the Russian Academy of Sciences, Prof., Dr. Sci. (Med.), President of N.V. Sklifosovsky Research Institute for Emergency Medicine; Head of the Department of Transplantology and Artificial Organs A.I. Yevdokimov Moscow State University of Medicine and Dentistry, https://orcid.org/0000-0002-0746-1884

20%, study design, the article text revision and approval

Evgeniy A. Tarabrin, Dr. Sci. (Med.), Head of the Scientific Department of Urgent Thoracoabdominal Surgery at N.V. Sklifosovsky Research Institute of Emergency Medicine, https://orcid.org/0000-0002-9616-1161

10%, analysis of the data obtained, the article text revision

Natalya K. Kuznetsova, Cand. Sci. (Med.), Anesthesiologist-Intensive Care Physician, Leading Researcher of the Anesthesiology Department, N.V. Sklifosovsky Research Institute for Emergency Medicine, https://orcid.org/0000-0002-2824-1020

10%, the article text revision

The article was received on May 17, 2021;
Approved after reviewing June 6, 2021;
Accepted for publication June 30, 2021