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ORIGINAL ARTICLE / ÖZGÜN MAKALE

Effects of intraoperative fluid therapy on intensive care process, morbidity, and mortality after lung transplantation

Akciğer nakli sonrasında intraoperatif sıvı tedavisinin yoğun bakım süreci, morbidite ve mortalite üzerine etkileri

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ABSTRACT

Background: This study aims to evaluate the effect of intraoperative fluid therapy on intensive care process and first 90-day morbidity and mortality in patients undergoing lung transplantation.

Methods: Between March 2013 and December 2020, a total of 77 patients (64 males, 13 females; mean age: 47.6±13.0 years; range, 19 to 67 years) who underwent lung transplantation were retrospectively analyzed. The patients were divided into two groups according to the amount of fluid given intraoperatively: Group 1 (<15 mL/kg^{-1}/h^{-1}) and Group 2 (>15 mL/kg^{-1}/h^{-1}). Demographic, clinical, intra- and postoperative data of the patients were recorded.

Results: Less than 15 mL/kg^{-1}/h^{-1} fluid was administered to 75.3% (n=58) of the patients (Group 1) and 24.7% (n=19) were administered more than 15 mL/kg^{-1}/h^{-1} (Group 2). In terms of native disease, the rate of diagnosis of chronic obstructive pulmonary disease and idiopathic pulmonary fibrosis was higher in Group 1, and the rate of other diagnoses was higher in Group 2 (p<0.01). The ratio of women in Group 2 was higher (p<0.05), while the body mass index values were significantly lower in this group (p<0.01). The erythrocyte, fresh frozen plasma, platelet, crystalloid and total fluid given in Group 2 were significantly higher (p<0.001). Inotropic/vasopressor agent use rates and extracorporeal membrane oxygenation requirement were significantly higher in Group 2 (p<0.01). Primary graft dysfunction, gastrointestinal complications, and mortality rates were also significantly higher in Group 2 (p<0.05).

Conclusion: The increased intraoperative fluid volume in lung transplantation is associated with primary graft dysfunction, gastrointestinal complications, and mortality rates.

Keywords: Intraoperative fluid assessment, lung transplantation, morbidity, mortality, native lung disease.

ÖZ

Amaç: Bu çalışmada akciğer nakli uygulanan hastalarda intraoperatif sıvı tedavisinin yoğun bakım süreci ve ilk 90 günlük morbidite ve mortalite üzerine etkisi değerlendirildi.

Çalışma planı: Mart 2013 - Aralık 2020 tarihleri arasında akciğer nakli yapılan toplam 77 hasta (64 erkek, 13 kadın; ort. yaş: 47.6±13.0 yıl; dağılım, 19-67 yıl) retrospektif olarak incelendi. Hastalar ameliyat sırasında verilen sıvı miktarına göre iki gruba ayrıldı: Group 1 (<15 mL/kg^{-1}/h^{-1}) ve Group 2 (>15 mL/kg^{-1}/h^{-1}). Hastaların demografik, klinik, ameliyat sırası ve sonrası verileri kaydedildi.

Bulgular: Hastaların %75.3'üne (n=58) 15 mL/kg^{-1}/h^{-1}'den az sıvı (Grup 1) ve %24.7'sine (n=19) 15 mL/kg-1/h-1'den fazla sıvı (Grup 2) uygulandı. Nativ hastalık açısından Grup 1'de kronik obstrüktif akciğer hastalığı ve idiyopatik pulmoner fibrozis tanısı oranı daha fazla iken, Grup 2'de diğer tanı oranı fazla idi (p<0.01). Grup 2'de kadın oranı daha fazla iken (p<0.05), bu grupta vücut kütle indeks değerleri anlamlı düzeyde düşük idi (p<0.01). Grup 2'de verilen eritrosit, taze donmuş plazma, trombosit, kristaloid ve toplam mayi anlamlı düzeyde yüksek idi (p<0.001). İnotropik/vazopressör ajan kullanım oranları ve ekstrakorporeal membran oksijenasyon gereksinimi Grup 2'de anlamlı düzeyde fazla idi (p<0.01). Grup 2'de primer greft disfonksiyonu, gastrointestinal komplikasyonlar ve mortalite oranları da anlamlı düzeyde yüksek idi (p<0.05).

Sonuç: Akciğer naklinde artmış intraoperatif sıvı hacmi primer greft disfonksiyonu, gastrointestinal komplikasyonlar ve mortalite oranları ile ilişkilidir.

Anahtar sözcükler: İntraoperatif sıvı değerlendirmesi, akciğer nakli, morbidite, mortalite, nativ akciğer hastalığı.

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Lung transplantation (LTx) is the final therapeutic option for end-stage lung diseases that have become oxygen-dependent, despite all medical treatment.[1] Since the first successful LTx in 1983, there have been many advancements in this field thanks to technological innovations and improving surgical techniques. Preoperative evaluation, intraoperative management, and postoperative follow-up are the most critical factors affecting the success of LTx. Early (postoperative 90-day) and late transplant success have mainly been linked to the intraoperative management of patients.[2] Some authors have associated intraoperative excessive intraoperative fluid administration with postoperative complications and mortality.[3,4] Several studies favor a restrictive fluid management strategy to limit pulmonary edema;[5] nevertheless, the effects of intraoperative restrictive versus liberal fluid therapy on postoperative outcomes in LTx still remain debated.[4]

In the present, study, we aimed to investigate the relationship between intraoperative fluid therapy and morbidity and mortality in LTx patients.

PATIENTS AND METHODS

This single-center, retrospective study was conducted at the University of Health Sciences, Ankara City Hospital, Department of Anesthesiology and Reanimation between March 2013 and December 2020. A total of 78 patients who underwent LTx were included. The patients were divided into two groups regarding the intraoperatively administered total crystalloid and colloid solutions and the amount of blood and blood products: Group 1 (<15 $mL/kg^{-1}/h^{-1}$) and Group 2 (>15 $mL/kg^{-1}/h^{-1}$).[6] Demographic and clinical data, intraoperative data, postoperative complications, duration of mechanical ventilation (MV), length of stay (LOS) in the intensive care unit (ICU) and hospital, and mortality rates were recorded for both groups. One patient who died intraoperatively was excluded from the study. Finally, a total of 77 patients (64 males, 13 females; mean age: 47.6±13.0 years; range, 19 to 67 years) were included in the study.

Anesthetic management

Premedication was not preferred due to low respiratory reserves. Since severe dyspnea may develop in the supine position, oxygen (O_2) was delivered through a face mask in the semi-sitting position. Vascular access was established with two 16-G intravenous cannulas. Lactated Ringer's solution (LR) was used as a maintenance fluid. Continuous systemic arterial monitoring was achieved via a five-lead electrocardiogram (ECG), pulse oximetry, and radial artery cannulation. The placement of the double-lumen tube (DLT) was confirmed with a fiberoptic bronchoscope (FOB). For intra- and postoperative systemic and pulmonary arterial pressure (PAP) monitoring, two central venous routes, one for the Swan-Ganz catheter, were established through the right internal jugular vein following intubation. A bispectral index (BIS) (BIS™, Covidien, MN, USA) sensor was placed on the patient's forehead to determine the depth of anesthesia. Anesthesia was induced in all patients by titrating 1 $\mu g/kg^{-1}$ of fentanyl, 0.15 mg/kg^{-1} of midazolam, and 1 to 2 mg/kg^{-1} of propofol. When the BIS became stable between 40 and 50, 0.6 mg/kg^{-1} of rocuronium bromide was administered to facilitate tracheal intubation. Following intubation, volume-controlled ventilation (VCV) was delivered at a tidal volume (TV) of 7 to 8 mL/kg^{-1} (ideal body weight) with a mixture of O_2/air (fraction of inspired oxygen, FiO_2: 0.5) and 5 cmH_2O positive end-expiratory pressure (PEEP). After switching to single-lung ventilation (SLV) following the transplantation of one lung, monitoring was continued in pressure-controlled ventilation (PCV) mode with titrated FiO_2 to maintain adequate arterial saturation (>92%), TV <6 mL/kg^{-1}, moderate PEEP, and inspiratory pressure <20 cmH_2O. The respiratory rate was adjusted to maintain the end-tidal carbon dioxide (CO_2) pressure in the range of 35 to 45 mmHg. During the maintenance of anesthesia, total intravenous anesthesia (TIVA) containing titrated remifentanil and propofol was administered. Besides, 0.2 mg/kg^{-1} of rocuronium bromide was infused approximately every 45 min throughout the operation to keep BIS between 40 and 60. The oropharyngeal temperature was monitored. While removing the lungs and sequentially placing the new lungs, norepinephrine (0.05 to 2 $\mu g/kg^{-1}/min$), which increases the systemic vascular resistance (SVR), was frequently administered to prevent hemodynamic fluctuations due to surgical manipulations or cold protective fluids filled into the thorax, particularly during the pulmonary arterial and venous anastomoses. The patients were administered liquid infusion to maintain the mean arterial pressure (MAP) at >65 mmHg, heart rate at 120 bpm, serum lactate level >2 mmol/L. The fresh frozen plasma (FFP), albumin 20%, and gelofusine® (B. Braun Melsungen AG., Melsungen, Germany) were preferred for volume expansion. Erythrocyte suspension was administered to keep the hemoglobin level >10 g/dL. Cell salvage was used to recover blood loss. At the end of surgery, the DLT was replaced with a single-lumen tube (SLT), and bronchoscopy was used to clear anastomotic lines and secretions. Before tube replacement, gastric contents were evacuated with a nasogastric or orogastric tube.

Then, the patient was transferred to the ICU under propofol and remifentanil infusion and appropriate monitoring. Extubation was performed after the patient responded consciously and took deep breaths on verbal command in the ICU.

Surgical procedure

A clamshell incision was performed in all patients undergoing double-LTx. In single-LTx, a sternum-sparing anterior thoracotomy incision was performed in the supine position. Following the incision, the thoracic cavity adhesions were released, and the lungs were fully mobilized. Subsequently, the pulmonary artery and vein stumps were prepared for implantation. After the arrival of the donor's lung to the operating room, pneumonectomy was performed, starting with the lung with poorer pulmonary function. Meanwhile, the patient's hemodynamics, PAP, and the contralateral lung pulmonary function were closely monitored until implantation, and extracorporeal membrane oxygenation (ECMO) was provided, if necessary. Following the sequential implantation of the donor's lungs, the clamps were removed, cold ischemia was terminated, and pulmonary function was evaluated by ventilation of the lungs. After checking the vascular anastomosis site for bleeding, and bronchial anastomosis site for air leak, the surgical procedure was completed by drain placement and chest closure. When ECMO or cardiopulmonary bypass (CPB) was required, heparinization was performed with an activated clotting time (ACT) in the range of 145 to 180. The Nipro® Membrane Oxygenator (Affinity® NT Integrated CVR/Membrane Oxygenator; Medtronic Inc., MN, USA) was used for ECMO support at 36°C and 1.5 to 2.4 L min/m^2 flow rate. The prime volume composition of the ECMO contained LR and other additives. The patients were admitted to the ICU either with or without postoperative support devices; i.e., central or peripheral venous-arterial (VA) ECMO.

Postoperative management

Early postoperative monitoring was a continuation of intraoperative monitoring. We targeted weaning the patients from MV at the earliest possible time to minimize ventilator-associated pneumonia and ventilator-associated lung injury. The amount of fluid to be administered was usually determined according to the restrictive approach, aiming to maintain the oncotic pressure. Immunosuppressive therapy was started. We evaluated the patients as per the standardized definition of primary graft dysfunction (PGD) by the International Society for Heart and Lung Transplantation (ISHLT), introduced in 2005 and updated in 2016 (Table 1).[7] Therefore, we decided on the treatment modalities according to the patients' partial pressure of oxygen (PaO_2)/FiO_2(P/F) ratios and chest radiographs at postoperative 6, 24, 48, 72 h.

Statistical analysis

Statistical analysis was performed using the IBM SPSS version 20.0 software (IBM Corp., Armonk, NY, USA). Descriptive data were expressed in mean ± standard deviation (SD) or median (min-max) for continuous variables and in number and frequency for categorical variables. The Shapiro-Wilk test was used to examine whether continuous data conforms to a normal distribution. The Student t-test or Mann-Whitney U test was performed to compare continuous variables between two groups. The chi-square and Fisher exact tests were used for group comparisons of categorical data. A p value of <0.05 was considered statistically significant.

RESULTS

All patients who underwent LTx were included in the study. Of the patients, 58 (75.3%) received intraoperative fluid <15 mL/kg^{-1}/h^{-1} (Group 1) and 19 (24.7%) received >15 mL/kg^{-1}/h^{-1} (Group 2). The mean amount of intraoperative fluid administered in Group 1 and Group 2 was 9.40±2.77 (range, 4.4 to 14.84) mL/kg^{-1}/h^{-1} and 19.27±3.47 (range, 15.11 to 27.40) mL/kg^{-1}/h^{-1}, respectively. There was no significant difference between the groups in terms of age, Lung Allocation Score (LAS), and Charlson Comorbidity Index (CCI) (p>0.05).

Table 1. The International Society for Heart and Lung Transplantation standardized definition of PGD

PGD stage	P/F ratio (mmHg)	Chest radiograph
0	>300	Normal
1	>300	Diffuse allograft infiltration/ pulmonary edema
2	200-300	Diffuse allograft infiltration/ pulmonary edema
3	<200	Diffuse allograft infiltration/ pulmonary edema

PGD: Primary graft dysfunction; P/F: PaO_2/FiO_2.

Table 2. Comparison of Group 1 and Group 2 demographic data

	Group 1 (n=58)					Group 2 (n=19)						
	n	%	Mean±SD	Median	Min-Max	n	%	Mean±SD	Median	Min-Max	Test statistic	*p*
Age (year)			49.0±12.4					43.0±13.9			t=1.788	0.078
BMI (kg/m^2)			23.1±3.9					20.3±3.7			t=2.696	**0.009**
Charlson Comorbidity Index			1.8±0.9	2	1-5			1.7±1.5	1	1-7	U=449.5	0.192
Lung Allocation Score			40.6±11.6	36.4	31.9-90.3			43.2±13.7	38.7	32.3-87.8	U=468.0	0.327
PAP (mmHg)			28.9±9.2	26	17-60			34.0±12.1	31	15-61	U=389.5	0.056
Native lung disease											χ^2=12.906	**0.003**
COPD	25	43.1				3	15.8					
Bronchiectasis	9	15.5				3	15.8					
IPF	15	25.9				2	10.5					
Others	9	15.5				11	57.9					
Sex											χ^2=7.161	**0.013**
Female	6	10.3				7	36.8					
Male	52	89.7				12	63.2					
Lung transplantation											χ^2=1.452	0.251
Double	53	91.37				15	78.9					
Single	5	8.62				4	20.05					

SD: Standard deviation; BMI: Body mass index; PAP: Pulmonary arterial pressure; COPD: Chronic obstructive pulmonary disease; IPF: Idiopathic pulmonary fibrosis.

Table 3. Distribution of native lung diseases in Group 1 and Group 2

	Group 1 (n=58)		Group 2 (n=19)	
Native disease	n	%	n	%
COPD	25	43.1	3	15.8
Bronchiectasis	9	15.5	3	15.8
Idiopathic pulmonary fibrosis	15	25.9	2	10.5
Histiocytosis X	1	1.7	2	10.5
Kartagener syndrome	0	0	2	10.5
Nonspecific interstitial pneumonitis	1	1.7	0	0
Silicosis	2	3.4	2	10.5
Pulmonary alveolar proteinosis	1	1.7	0	0
Slicoscleroderma/erasmus send	0	0	1	5.3
Rejection	0	0	1	5.3
Necrotizing pneumonia	1	1.7	0	0
Lymphangioleiomyomatosis	1	1.7	1	5.3
Cystic fibrosis	0	0	1	5.3
Pleuroparenchymal fibroelastosis	1	1.7	0	0
Interstitial lung disease	1	1.7	0	0
Idiopatic pulmonary hemosiderosis	0	0	1	5.3

COPD: Chronic obstructive pulmonary disease.

The body mass index (BMI) values in Group 2 were significantly lower than Group 1 ($p<0.01$). We observed a significant difference in the native lung disease distribution between the groups ($p<0.01$). Group 1 was more likely to have a chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), while Group 2 had rare disorders more commonly, such as histiocytosis X, silicosis, Kartagener's syndrome, pulmonary hemosiderosis, cystic fibrosis, lymphangioleiomyomatosis, rejection, and scleroderma. There was a significant difference in the sex ratio between the two groups ($p<0.05$), and the rate of female patients was higher in Group 2. Single or double-LTx rates were similar between the groups ($p>0.05$) (Table 2). Table 3 shows the distribution of native lung diseases according to the groups.

There was no significant difference in the intraoperative MAP values between the groups. However, we found a significantly higher mean amount of FFP, red blood cell components (RBCCs), platelet concentrate (PC), crystalloids, and total fluid administered in Group 2 ($p<0.001$). The mean amount

Table 4. Comparison of Group 1 and Group 2 intraoperative variables

	Group 1 (n=58)			Group 2 (n=19)				
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Test statistic	*p*
MAP	74.9±6.2			77.0±6.2			t=-1.286	0.202
FFP (U)	10.9±3.3			15.0±4.3			t=-4.415	**0.000**
RBCC (U)	3.1±2.4	3	0-10	7.8±2.2	8	4-12	U=89.5	**0.000**
PC (U)		0	0-2		1	0-4	U=261.0	**0.000**
Crystalloid (mL)	1,964.7±851.3	2000	400-4,500	2,531.6±948.1	2500	500-4.000	U=330.5	**0.009**
Colloid (mL)	56.9±180.8	0	0-1,000	179.0±406.3	0	0-1.500	U=469.5	0.127
Total volume (mL)	6,400.0±1,880.3	6125	3,550-11,400	10,244.7±2,418.4	9800	6.450-16.200	U=106.0	**0.000**
Urine (mL)	1,039.9±739.5	800	100-4,200	830.5±1,034.0	500	60-3.700	U=328.5	**0.008**

SD: Standard deviation; MAP: Mean arterial pressure; FFP: Fresh frozen plasma, RBCC: Red blood cell component; PC: Platelet concentrate.

Table 5. Comparison of Group 1 and Group 2 morbidity and mortality rates

	Group 1 (n=58)		Group 2 (n=19)			
	n	%	n	%	Test statistic	*p*
Inotrope/vazopressor						
0-1	51	87.9	10	52.6	χ^2=11.282	**0.006**
2-3	7	12	9	47.4		
ECMO	26	44.8	16	84.2	χ^2=8.953	**0.003**
Preoperative ECMO	2	7.69	0	0.0		
Preoperative MV	2	3.44	1	5.26		
Complications						
Cardiovascular system	1	18	7	36.8	χ^2=0.220	0.639
Respiratory system	14	24.1	9	47.4	χ^2=3.684	0.055
Acute kidney injury	9	15.5	6	31.6	χ^2=2.354	0.180
PGD	16	27.6	11	57.9	χ^2=5.774	**0.016**
0 -1 PGD	46	79.3	9	47.4	χ^2=7.125	**0.017**
2-3 PGD	12	20.7	10	52.6		
Neurological system	16	27.6	4	21.1	χ^2=0.318	0.765
Gastrointestinal system	0	0	3	15.8	χ^2=9.529	0.013
Endocrine system	4	6.9	0	0	χ^2=1.382	0.567
Bleeding/revision	9	15.5	4	21.1	χ^2=0.312	0.725
Mortality	3	10	7	36.8	χ^2=5.160	0.033

ECMO: Extracorporeal membrane oxygenation; MV: Mechanical ventilation; PGD: Primary graft dysfunction.

of colloid use was similar in both groups (p>0.05). However, we observed a significant difference in the intraoperative urine output between the groups (p<0.001), which was lower in Group 2 (Table 4).

The amount of inotropic and vasopressor agents used and ECMO requirement were significantly higher in Group 2 (p<0.01), as well as PGD development, gastrointestinal (GI) complications, and mortality rates (p<0.05) (Table 5).

We observed no significant difference between the groups in terms of the mean operative time, duration of MV, and LOS in the ICU and hospital (p>0.05) (Table 6).

DISCUSSION

The present study showed that excess intraoperative fluid administration was associated with higher postoperative PGD and mortality rates (p<0.01). The rate of Grade 2 and 3 PGD was 20.7% (n=12) in Group 1, which is consistent with the literature,[8] but 52.6% (n=10) in Group 2. Several authors have reported that excessive fluid therapy leads to organ dysfunction. Geube et al.[3] found that increased intraoperative fluid volume was associated with severe PGD after LTx. In the current study, the PDG-related mortality rate in Group 2 was almost three times higher than in Group 1. In another study,

Table 6. Comparison of Group 1 and Group 2 operative times, MV, LOS in ICU and hospital

	Group 1 (n=58)			Group 2 (n=19)				
	Mean±SD	Median	Min-Max	Mean±SD	Median	Min-Max	Test statistic	*p*
Operative time (min)	619.9±99.4	600	480-1,080	596.6±96.1	600	435-795	U=477.0	0.378
Duration of MV (h)	137.8±232.5	26.5	11-1,104	345.4±503.7	96	0-1,680	U=412.5	0.102
LOS in ICU (day)	14.5±9.5	12	4-51	30.1±30.1	18	0-96	U=401.5	0.077
Hospital length of stay (day)	32.3±18.2	27.5	4-119	45.0±33.1	38	0-120	U=435.0	0.170

SD: Standard deviation; MV: Mechanical ventilation; LOS: Length of stay; ICU: Intensive care unit.

Christine et al.[9] reported that mortality was eight times higher among patients who developed PGD after LTx.

Increasing evidence in the literature suggests that intraoperative therapy in LTx may affect postoperative outcomes. Nevertheless, no clinical guidelines are available for perioperative management, yet. Comprehensive data are lacking on the most critical aspects of perioperative management, including induction and maintenance of anesthesia, hemodynamic monitoring and management, mechanical support, fluid therapy, anti-inflammatory and anticoagulant therapies, and ventilation strategies.[10]

Myles et al.[11] reported a similar rate of one-year disability-free survival, but significantly higher acute kidney injury and surgical site infection with the restrictive approach in major abdominal surgeries.[11] In the present study, only GI complications were significantly more frequent in Group 2. In contrast, the rates of the respiratory system, renal, and cardiovascular complications showed no statistically significant difference, despite being almost two-fold higher in Group 2. Unlike Myles et al.,[11] the mortality rate was higher among our patients in Group 2, which may be explained by the higher amount of fluid administered in the restrictive therapy group and different surgery techniques performed.

Early negative fluid balance has been associated with lower mortality in patients following cardiovascular surgery.[12] Recent studies have also argued that personalized fluid administration and zero-balance therapy may yield improved outcomes.[13]

Lung transplantations are surgeries that can take 8 to 15 h depending on single or double replacement, comorbidities, and complications. The procedure is completed to a large extent without any support (cardiac pump or ECMO), and the heart is exposed to various manipulations meanwhile. As a result, hemodynamic fluctuations can occur, and boluses of crystalloids and colloids are required, along with inotropes and vasopressors, to achieve optimal hemodynamics. In addition, varying degrees of pulmonary edema may occur in the newly-transplanted lung due to ischemia-reperfusion injury, increased vascular permeability, and impaired lymphatic drainage. Furthermore, oxygenation impairment may induce a series of complications, starting with pneumonia. Studies have demonstrated that a restrictive fluid management strategy can prove beneficial in limiting pulmonary edema.[5] On the other hand, appropriate fluid resuscitation is necessary to ensure hemodynamic optimization and maintain adequate organ perfusion. Achieving this delicate balance may help to prevent postoperative complications. In our study, the mean amount of intraoperative fluid administered was 9.40±2.77 $mL/kg^{-1}/h^{-1}$ in 75.3% of the patients and 19.27±3.47 $mL/kg^{-1}/h^{-1}$ in 24.7%. In addition, COPD and IPF occurred more frequently in the patients administered on less fluid. In contrast, the patients with a large volume of fluid therapy were primarily women, had lower BMI values, and developed rare lung diseases after LTx. Presumably, autoimmunity plays a role in the etiology of these native lung diseases. On the other hand, low BMI frequently occurs due to prolonged waiting times for LTx, acute exacerbations, and malnutrition.

Intraoperative transfusion of RBCCs and plasma in LTx is linked with PGD.[14] Geube et al.[3] indicated a correlation between total fluid therapy and Grade 3 PGD in LTx, but no correlation between non-blood components and the disease. The authors concluded that each liter of intraoperative fluid increased the rate of Grade 3 PGD by 22%. A meta-analysis associated high intraoperative fluid administration with Grade 3 PGD and excessive blood products with PGD and mortality.[15] In the present study, RBCCs, FFP, and total fluid administered were significantly higher in Group 2 and correlated with PGD and mortality.

In their study, Mcllroy et al.[16] investigated the link between anesthetic management variables and early PGD by assessing 107 LTx cases and reported a 42 mmHg decrease in the P/F ratio for each 2.7-fold increase in colloid volume, associating colloid therapy with prolonged duration of MV and lower postoperative oxygenation. In contrast, we found no significant relationship between colloid therapy and morbidity and mortality in our study population.

Many authors recommend using more than one inotropic or vasopressor agent along with restrictive intravenous fluid to ensure hemodynamic optimization.[5] In the present study, the rate of using more than one inotropic or vasopressor agent was higher among patients with higher fluid administration. That was also the case for ECMO requirements. We intraoperatively decided that hemodynamic optimization could not be achieved through SLV and continued the surgery with ECMO support in these patients. We considered native lung disease culpable in these cases due to previous infections and adhesions, as well as autoimmunity.

Bittner et al.[17] reported a higher incidence of hemorrhage with ECMO and worse outcomes with blood products administration. A previous study showed no effect of RBCC and FFP administration on survival in LTx with CPB or ECMO and associated only high amounts of PC with early mortality.[18] In the present study, Grade 2 and 3 PGD was more frequent among patients receiving high amounts of crystalloids, blood, and blood products (Group 2). The development of pulmonary edema can be explained by the damage to the protective glycocalyx structure due to surgical trauma, ischemia-reperfusion injury, impaired lymphatic drainage, and increased glycocalyx permeability depending on the amount of fluid administered and solute content. Besides, ECMO's disadvantages, such as the requirement of priming solutions, heparinization, and more blood, may have played a role in pulmonary edema. On the other hand, we observed less urine output in Group 2, despite more fluid administered. This may have resulted from fluid leakage into the extravascular space, ECMO applied during transplantation, or renal involvement in the primary pathology. Although the candidates on the waiting list undergo pre-transplant renal evaluation, including a creatinine clearance test, their renal functions may significantly decline during the complex surgical procedure.

The current study showed that a high amount of intraoperative fluid administration might be also associated with GI complications. A previous study reported a shorter healing process with tissue perfusion after 6 h of anesthesia recovery and restrictive fluid management in patients undergoing colon resection.[19] However, Pang et al.[20] reported that intestinal perfusion was adversely affected as the fluid amount in restrictive therapy decreased. Several studies have reported abdominal complications of varying severity at a rate of 21 to 62% after LTx.[21,22] Prolonged operative time, postoperative epidural analgesia, immunosuppressive drugs, and electrolyte imbalance play a role in these complications.[23] In the present study, the rate of GI complications was higher among patients receiving a higher amount of fluid (Group 2).

Nonetheless, our study has several limitations. First, it has a retrospective design. Second, homogeneous patient groups are lacking due to the small scale of our center. Third, the event rate and sample size are insufficient to perform multivariate analysis. On the other hand, evidence is insufficient in the published literature to investigate the relationship between intraoperative fluid therapy and postoperative outcomes in LTx. Therefore, we believe that our study provides valuable contributions to the body of knowledge in the literature.

In conclusion, intraoperative fluid management in lung transplantation is associated with primary graft dysfunction, gastrointestinal complications, and mortality. We consider that intravenous fluids, inotropes, and vasopressors administered to ensure optimal intraoperative hemodynamics, along with native lung diseases, are crucial for postoperative morbidity and mortality. Further large-scale, prospective, randomized studies are required to elucidate the relevant interactions at play.

Ethics Committee Approval: The study protocol was approved by the the University of Health Sciences, Ankara City Hospital Ethics Committee (date: 17.03.2021, no: E1/1630/2021). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

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