Renal Replacement Therapy

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Comparison of estimated blood loss during living kidney transplantation according to the number of double-filtration plasmapheresis

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Abstract

Background Plasmapheresis is an important preoperative desensitization treatment for ABO-incompatible living kidney transplantation. However, in cases with plasma exchange therapy (PET), it is necessary to consider the risks of perioperative bleeding and healthcare economic costs. This study investigated the association between intraoperative blood loss and the frequency of preoperative double-filtration plasmapheresis (DFPP) and explored the correlation between DFPP frequency and coagulation factors. Furthermore, the study examined the incidence of perioperative bleeding complications.

Methods We enrolled 294 patients (205 men and 89 women) who underwent living kidney transplantation at our institution between January 2020 and March 2023, without PET or with only DFPP performed as PET. A single dose of rituximab (200 mg) was administered to ABO-incompatible living kidney transplant patients within 7 days before transplantation. In these patients, PET was performed until anti-blood group IgG and IgM antibody titers were reduced to 32 times or less.

Results The intraoperative blood loss increased in accordance with the DFPP sessions. The amount of bleeding significantly increased when DFPP was performed ≥ 2 sessions. Considering this, we initiated serum fibrinogen level measurements from the middle of the study and observed that serum fibrinogen levels decreased in correlation with the number of DFPP sessions. Fibrinogen levels dropped to critical levels (< 100 mg/dL) after three sessions of DFPP. Within the entire cohort, four patients (1.4%) underwent post-transplantation hematoma removal surgery, and among them, three had received DFPP before transplantation.

Conclusions The number of DFPP procedures was associated with the amount of bleeding and serum fibrinogen levels during living kidney transplantation.

Keywords ABO incompatible, Double-filtration plasmapheresis, Fibrinogen, Kidney transplantation

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Background

Preoperative apheresis therapy is important before kidney transplantation, and plasma exchange therapy (PET) is considered one of the most important preoperative treatments for ABO-incompatible living kidney transplantation (ABO-ILKT) [1]. PET in ABO-ILKT aims to prevent the early onset of acute antibody-mediated rejection (AMR) and thrombotic microangiopathy (TMA), which can occur shortly after transplantation, as well as suppress any excessive production of blood-type antibodies after ABO-ILKT. In our institution, we perform preoperative apheresis based on a cutoff value of ≤32 times of IgG and IgM anti-blood type antibody titers [2–4]. Our treatment modalities include double-filtration plasmapheresis (DFPP) and plasma exchange (PEX). While preoperative PET is important for desensitization, it may present difficulties in terms of intraoperative bleeding for surgeons. Moreover, allergic reactions to fresh frozen plasma (FFP) supplementation during PEX and healthcare economic costs were also encountered. In this study, we aimed to elucidate the relationship between intraoperative blood loss and the number of DFPP sessions before living kidney transplantation. Based on these findings, we initiated serum fibrinogen level measurements on the day of surgery and further investigated the correlation between the frequency of DFPP sessions and serum fibrinogen levels. Furthermore, we examined perioperative bleeding complications.

Materials and methods

Patients and design

We reviewed patient data obtained from the patient medical records. This retrospective study enrolled 294 patients who underwent living kidney transplantation at our institution between January 2020 and March 2023, without PET or with only DFPP performed as PET.

Immunosuppressive regimens and desensitization protocols

All patients received a triple immunosuppressive treatment comprising a calcineurin inhibitor, an antimetabolic agent, and methylprednisolone starting 1 week before surgery. Basiliximab was administered intravenously as an induction therapy at a dose of 20 mg on days 0 and 4. Rituximab was administered as a single dose (200 mg) within 7 days before transplantation for ABO-ILKT [1]. To remove anti-A/B antibodies, the patients underwent a few sessions of DFPP before transplantation. These apheresis sessions were performed until blood type IgG and IgM antibody titers decreased to a level of 1:32 or below [2, 3, 5].

Statistical analysis

Continuous variables are shown as the mean ± standard deviation. Categorical variables are presented as frequencies and percentages. The Mann–Whitney *U* test was used to compare patient characteristics between groups categorized by the number of DFPP sessions. All analyses were conducted using JMP PRO 15.0.0 software (SAS Institute, Cary, NC, USA), and *P*-values of < 0.05 denoted statistical significance.

Results

Patient population and patient characteristics

Table 1 presents the patient characteristics of the 294 individuals in this study, categorized by the number of DFPP sessions. The number of patients in each group, based on the frequency of preoperative DFPP sessions, were as follows: 216 cases had no sessions, 34 cases had one session, 31 cases had two sessions, and 13 cases had three or more sessions. Of the 78 patients who underwent preoperative DFPP, 56 of them underwent ABO-ILKT. Of the 294 recipients, 36 (12.2%) continued to take antiplatelet agents because of complications and underwent surgery.

Surgical data

Table 2 displays the surgical data categorized by the number of DFPP sessions. We observed no significant differences in operative time, warm ischemic time, or total ischemic time among the four groups.

Relationship between the number of DFPP sessions and intraoperative blood loss

We focused on the relationship between intraoperative blood loss and the number of DFPP sessions. Intraoperative blood loss was significantly increased in DFPP cases compared to cases in which DFPP was not performed and associated with the number of DFPP sessions (not performed: 168 ± 279 mL; versus 1 session: 200 ± 146 mL, $p = 0.5581$; versus 2 sessions: 327 ± 323 mL, $p = 0.0053$; versus ≥ 3 sessions 392 ± 559 mL, $p = 0.0073$; Fig. 1).

Relationship between the number of DFPP sessions and serum fibrinogen level

To investigate the association between the number of DFPP sessions and coagulation factor loss, we measured the preoperative fibrinogen levels on the day of surgery in the middle of the study period. Fibrinogen levels decreased significantly with the increased number of DFPP sessions (not performed: 295 ± 83 mg/dL; versus 1 session: 160 ± 25 mg/dL, $p < 0.001$; versus 2

Table 1 Patient characteristics categorized by the number of DFPP sessions

	0 (*n* = 216)	**1 (*n* = 34)**	**2 (*n* = 31)**	**≥ 3 (*n* = 13)**	***P***
Age (years)	49 ± 14	51 ± 15	50 ± 14	56 ± 12	0.3436
Sex (M/F)	159/57	22/12	19/12	5/8	0.0291
Body mass index (kg/m^2)	22.7 ± 4.1	22.4 ± 3.1	22.5 ± 5.0	21.9 ± 7.8	0.9238
Primary cause of ESRD					0.0194
Diabetic nephropathy	59 (27.3%)	7 (20.6%)	8 (25.8%)	2 (15.4%)	
IgA nephropathy	43 (19.9%)	5 (14.7%)	6 (19.4%)	1 (7.7%)	
Nephrosclerosis	11 (5.1%)	8 (23.5%)	1 (3.2%)	2 (15.4%)	
ADPKD	10 (4.6%)	3 (8.8%)	4 (12.9%)	0 (0%)	
Others (including unknown primary disease)	93 (43.1%)	11 (32.4%)	12 (38.7%)	8 (61.5%)	
ABO-ILKT/ABO-CLKT	17/199	28/6	21/10	7/6	< 0.001
DSA (+)	10 (4.6%)	5 (14.7%)	8 (25.8%)	8 (61.5%)	< 0.001
Continuation of antiplatelet agents at surgery	26 (12.0%)	4 (11.7%)	4 (12.9%)	2 (15.4%)	0.9855
Donor age (years)	60 ± 10	59 ± 9	59 ± 11	64 ± 9	0.5131
Donor sex (M/F)	55/161	12/22	11/20	7/6	0.0894

ABO-CLKT, ABO-compatible living kidney transplantation; ABO-ILKT, ABO-incompatible living kidney transplantation; ADPKD, autosomal dominant polycystic kidney disease; DSA, donor-specific antibody; ESRD, end-stage renal disease

Table 2 Surgical data categorized by the number of DFPP sessions

	0 (*n* = 216)	**1 (*n* = 34)**	**2 (*n* = 31)**	**≥ 3 (*n* = 13)**	**P**
Operative time (min)	257 ± 50	273 ± 50	275 ± 57	262 ± 75	0.1662
Warm ischemic time (s)	229 ± 85	228 ± 87	246 ± 66	287 ± 124	0.0933
Total ischemic time (min)	72 ± 23	73 ± 21	71 ± 21	64 ± 15	0.6188

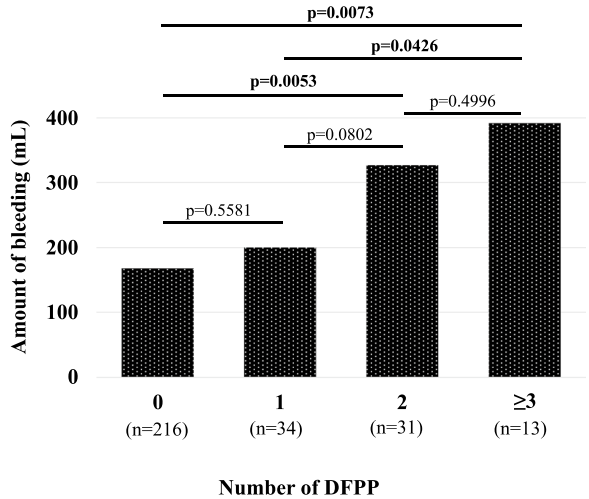

Fig. 1 Number of double-filtration plasma exchange (DFPP) procedures and intraoperative blood loss. The amount of bleeding significantly increased when DFPP was performed ≥ 2 times

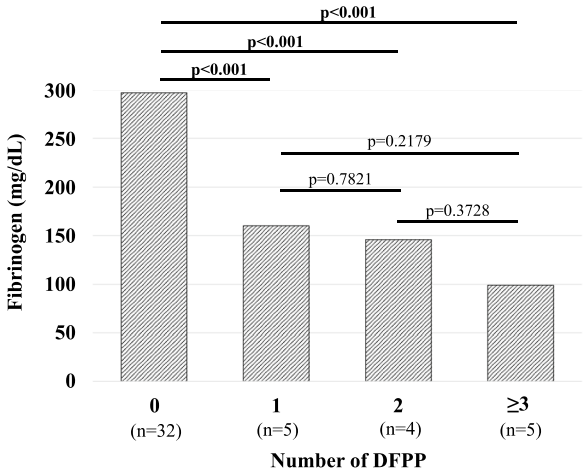

Fig. 2 Number of DFPP procedures and serum fibrinogen level on the day of surgery. Serum fibrinogen dropped to critical levels (≤ 100 mg/dL) after three DFPP sessions

Table 3 Four patients who underwent hematoma removal surgery

	Age	Sex	Preoperative PET	Continuation of antiplatelet agents	Blood loss at transplant	Timing of hematoma removal surgery
1	38	F	DFPP × 2	Without	263 mL	POD5
2	43	M	DFPP × 1	Without	726 mL	Same day at transplant
3	27	M	N/A	Without	166 mL	POD3
4	36	M	DFPP × 2	With	750 mL	POD7

PET, plasma exchange therapy; POD, postoperative day

sessions: 146 ± 76 mg/dL, $p < 0.001$, versus ≥ 3 sessions: 99 ± 59 mg/dL, $p < 0.001$; Fig. 2).

Postoperative hematoma removal surgery

Postoperative hematoma removal surgery was performed in four patients (1.4% of the total), of which three underwent preoperative DFPP (Table 3). In all of these cases, the bleeding sites were not at the vascular anastomoses or subcapsular hematomas but originated from the transplanted kidney bed or the muscle layer at the incision site. The time in which these four cases underwent hematoma removal surgery was a period when routine preoperative serum fibrinogen measurements were not conducted. As a result, the fibrinogen levels on the day of surgery in these cases remain unknown.

Discussion

ABO-ILKT presents numerous unresolved issues, including the occurrence of TMA. Regarding anti-blood-type antibody titers, even during the era when splenectomy was performed for antibody removal, some patients exhibited stable clinical courses despite having relatively high antibody titers. However, some patients would develop severe AMR despite having low titers. Currently, there is a lack of evidence beyond traditional antibody titer measurements to determine cases not requiring preoperative PET. Therefore, at our institution, we perform preoperative PET until anti-blood-type antibody titers are reduced to 32 times or less, considering a previous report [6]. This approach is adopted to minimize the risk associated with ABO-ILKT.

This study focused on DFPP, a routine desensitization therapy for living kidney transplant recipients such as ABO-ILKT. Initially, we examined cases in which only DFPP was administered as part of the pretransplant desensitization therapy. The volume of intraoperative bleeding increased as a function of the number of DFPP sessions. As we initiated the measurement of serum fibrinogen levels on the day of surgery starting from the middle of the study, it became evident that serum fibrinogen levels decreased in accordance with the number of DFPP sessions. Specifically, fibrinogen dropped to critical levels (< 100 mg/dL) after three DFPP sessions [7, 8]. Subsequently, regardless of the number of DFPP sessions, hematoma removal surgery was performed in four cases. Among these four patients, three underwent DFPP sessions as part of their pre-transplant treatment. Unexpectedly, none of the patients who underwent DFPP three times or more required postoperative hematoma removal surgery. We conclude that administering FFP from the beginning of surgery in cases with a high number of DFPP sessions helps reduce the amount of bleeding.

There are three types of apheresis modalities: DFPP, PEX, and plasma absorption [9–11]. In Japan, DFPP and PEX are used for antibody removal, and insurance covers up to four preoperative and two postoperative DFPP sessions for ABO-incompatible and lymphocyte antibody-positive living kidney transplants. DFPP is a therapeutic method involving two-stage plasma processing, separated by plasma-separation membranes, including an ultrafine (small-pore size) separation membrane (plasma component fractionator). Because of they have higher molecular weights than albumin, most coagulation factors are eliminated by DFPP and PEX using albumin solution as a substitution fluid [12–14]. Albumin is used as a replacement fluid; therefore, DFPP is less likely to induce allergic reactions than PEX using FFP as a replacement fluid and is more economical. However, performing DFPP immediately before transplantation surgery can increase the risk of bleeding because of reduced coagulation factors, low plasma protein levels caused by albumin leakage, and debilitated defense against infection due to lower complement and immunoglobulin levels.

In recent years, selective plasma exchange (SePE), a modified form of PEX, has been used as an effective PET in ABO-ILKT [15]. In SePE, a secondary membrane utilized in DFPP is employed as a plasma-separation membrane. This plasma-separation membrane is designed with pore sizes set to range between the molecular weight of fibrinogen (approximately 320,000) and IgG (approximately 160,000). Using such a membrane, it becomes possible to retain molecules such as fibrinogen and coagulation factor XIII (with a molecular weight of approximately 320,000) within the plasma while removing substances with molecular weights smaller than IgG. This approach offers the advantage of minimizing the

removal of coagulation factors. Moreover, SePE can be performed using albumin replacement, resulting in fewer side effects compared with PEX using FFP. Additionally, albumin is more cost-effective than FFP, providing medical–economic benefits [16]. When comparing the cost of replacement fluids in a single session of PEX and SePE, the cost of albumin replacement fluid in SePE is at least one-third less expensive compared with PEX, which uses FFP as the replacement fluid. However, its efficacy in reducing anti-blood-type antibodies is inferior to those of DFPP and PEX. Currently, for patients undergoing ABO-ILKT, we implement a preoperative desensitization-therapy approach using a combination of DFPP and SePE, considering the underlying disease and anti-blood-type antibody titers. A preoperative desensitization protocol combining DEPP and SePE is currently under development. This study had some limitations. First, the amount of intraoperative bleeding during the kidney transplantation surgery could have been influenced by factors apart from bleeding tendency, such as the complexity of vascular anastomosis procedures. For instance, surgeries involving multiple renal arteries or requiring complex sutures, such as conjoint methods, may result in additional bleeding, necessitating further sutures. Second, this was a single-center retrospective study with a possibility of selection bias.

Conclusions

Our present study demonstrated that the number of DFPP procedures was associated with the amount of bleeding and fibrinogen levels. It is crucial to consider the preoperative desensitization protocol with an understanding of the strengths and weaknesses of DFPP.

Abbreviations

ABO-CLKT	ABO-compatible living kidney transplantation
ABO-ILKT	ABO-incompatible living kidney transplantation
AMR	Acute antibody-mediated rejection
DFPP	Double-filtration plasmapheresis
FFP	Fresh frozen plasma
PET	Plasma exchange therapy
PEX	Plasma exchange
SePE	Selective plasma exchange
TMA	Thrombotic microangiopathy

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Author contributions

TY was a major contributor in writing the manuscript. TY, TK, and YF collected the data. TY, TK, YF, TB, AS, RO, KU, TH, KO, NH, HI, and TT contributed to patient treatment, related discussions, and reviewed the manuscript. All authors reviewed and edited the manuscript and approved the final version.

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Availability of data and materials

The datasets used and/or analyzed in the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This retrospective study was approved by the Institutional Ethics Committee of the Tokyo Women's Medical University (ID: 4460-R). This study was conducted in accordance with the Declaration of Helsinki and the Istanbul Declaration regarding donor sources.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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