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**Safety and efficacy of tandem hemodialysis and selective plasma exchange in
pretransplant desensitization of ABO-incompatible kidney transplantation**

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Short title: Tandem HD and SePE therapy

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Abstract

Introduction: In patients requiring both hemodialysis (HD) and apheresis, the two treatments can be performed simultaneously. At our hospital, selective plasma exchange (SePE) is often performed along with HD for removal of isoagglutinins before ABO-incompatible kidney transplantation. The two treatments can be completed within the HD schedule, which allows the treatment time to be shortened. This approach is also less stressful for patients because fewer punctures are required. In this study, we investigated the safety and efficacy of tandem HD and SePE.

Methods: A total of 58 SePE sessions in 30 ABO-incompatible kidney transplant recipients were investigated. The SePE circuit was connected in parallel with the HD circuit, and tandem HD and SePE therapy was performed using filtration methods. The SePE sessions were divided into two groups: those with SePE monotherapy (group S, n=20) and those with tandem therapy (group T, n=38). Changes in transmembrane pressure (TMP), arterial pressure (AP), venous pressure (VP) and decrease in isoagglutinin titers over time were compared between the groups with adjustment for background data.

Results: The internal pressures (AP and VP) were higher in group T, and there were significant differences in changes of TMP and AP over time between groups T and S. Membrane exchange was required in one case in group T due to coagulation. There was a more significant decrease of immunoglobulin G isoagglutinin titers in group T compared to group S. No case had antibody-mediated rejection after transplantation.

Discussion/Conclusion: In HD/SePE tandem therapy, internal pressures were higher and TMP and AP tended to increase more compared to SePE monotherapy, but we were able to perform the two treatments without any functional problems. Tandem therapy was also effective in decreasing isoagglutinin titers, which suggests that this may be a beneficial treatment modality as apheresis before ABO-incompatible kidney transplantation.

Introduction

Pre-transplant apheresis has become less common in ABO-incompatible (ABOi) kidney transplantation for patients with already low isoagglutinin titers or those successfully desensitized by immunosuppressants such as rituximab[1-6]. However, multiple sessions of apheresis are still performed for isoagglutinin removal in some patients[7-11].

Selective plasma exchange (SePE) is a new simple PE modality that uses a membrane plasma separator with a smaller pore size compared to conventional plasma separators, and enables removal of small and medium-sized molecules without removing larger substances such as coagulation factors[12]. SePE has increasingly been shown to be effective in cases in which an etiologic agent requires removal[13-16], since it causes fewer side effects due to use of albumin as the substitution fluid, in contrast to use of fresh frozen plasma (FFP) in PE. SePE also has a cost benefit because albumin is cheaper than FFP. Since 2015, we have used SePE for pretransplant apheresis in ABOi kidney transplantation, with favorable results[17, 18].

In patients requiring both hemodialysis (HD) and apheresis, the two treatments can be performed simultaneously. At our hospital, SePE is often performed along with HD for isoagglutinin removal before ABOi kidney transplantation[17, 18]. The two treatments can be completed within the HD schedule, which allows a shorter treatment time. This approach is also less stressful for patients because fewer punctures are required. The safety and efficacy of tandem HD and PE have been shown[19-29], but there are few reports on tandem HD and SePE therapy. In this study, we investigated the safety and efficacy of this therapy.

Patients and Methods

Study design and participants

A retrospective, case-series study was conducted in patients with end-stage renal disease who underwent ABOi kidney transplantation with apheresis therapy from January 2015 to December 2018 at Osaka City University Hospital (These patients were derived from our previous studies [17,18].). The inclusion criteria were kidney transplant recipients (KTRs) who had undergone at least one session of SePE. Patients with donor-specific antibodies were excluded. A total of 58 SePE sessions in 30 ABOi KTRs were examined in the study. The sessions were divided into those with SePE monotherapy (group S, n=20) and those with tandem therapy (group T, n=38).

This study protocol was conducted in accordance with the Principles of the Declaration of Helsinki and the Declaration of Istanbul and was approved by the ethics committee of Osaka City University Graduate School of Medicine (No. 4009). Opt-out consent was obtained instead of written informed consent; i.e., we provided patients with information explaining the proposed project (purpose, required individual data, and duration of the study) by means of an information sheet or hospital website and gave them the opportunity to opt out.

Desensitization protocols

Our desensitization protocols have been reported elsewhere[4, 30]. The full protocols are available in the **Supplemental Material**. In brief, desensitization was conducted by immunosuppressive therapy and apheresis to reduce pretransplant isoagglutinin titers (immunoglobulin G (IgG) and IgM) to $\leq 1:16$ [4, 30].

Conditions for performing SePE

Conditions for performing SePE were derived from our previous studies[17, 18]. Full details are given in the **Supplemental Material**. In brief, SePE was performed using a KM-9000 (Sanyo Electronic Industries Co., Ltd. Okayama, Japan), TR55X (Toray Medical Co.,

Ltd. Tokyo, Japan) or ACH-Σ (PlasautoΣ in overseas models) (Asahikasei Medical Co., Ltd. Tokyo, Japan) blood purification system and an Evacure Plus EC-4A10 (Evaclio, EC-4C in overseas models) (Kawasumi Laboratories, Inc., Tokyo, Japan) selective plasma separator[31]. During SePE, the quantity of blood flow (QB) was maintained at 100 ml/min with a plasma separation rate of 30 ml/min. The target processed plasma volume (PV) was set at 2 PV. In tandem HD and SePE therapy, SePE was performed in parallel with the HD circuit (Figure 1[17]) (QB and plasma separation rate were the same as in SePE monotherapy at 100 ml/min and 30 ml/min, respectively), and QB (tandem HD) was calculated using the following equation: $QB \text{ (tandem HD)} = QB \text{ (original HD)} - QB \text{ (SePE)}$.

After HD was initiated, apheresis treatment was started by connecting the apheresis circuit, which was connected to the blood removal side sample port of the HD circuit and the liquid level adjustment line of the arterial chamber.

As the anticoagulant, unfractionated heparin or nafamostat mesilate was used according to the patient condition. In SePE monotherapy, when using unfractionated heparin, we initially infused 2000 units intravenously followed by a maintenance infusion of 1000 units/h, and when using nafamostat mesilate, we administered a maintenance infusion of 25 mg/h. In tandem HD and SePE therapy, heparin was administered from the dialysis circuit alone (initial intravenous infusion of 2000 units followed by a maintenance infusion of 1000 units/h), while nafamostat mesilate was administered from both the dialysis and apheresis circuits (maintenance infusion of 25 mg/h for each circuit). In both instances, the dose was increased when there was much residual blood or circuit clotting. Blood was returned after apheresis treatment, and the apheresis circuit was disconnected.

The substitution fluid was normally 5% albumin, but in recipients with decreased coagulation factors, 5% albumin was first used as 3/4 of the total volume, followed by FFP as the remaining 1/4 of the volume. SePE was normally completed within the 4-hour HD time

in Group T, but the HD time was extended if the total volume of replacement fluid was large.

Measurement of clinical data

Clinical data were determined as described previously[17]. The details are shown in the **Supplemental Material**. Changes of transmembrane pressure (TMP), arterial pressure (AP) and venous pressure (VP) over time were determined from medical records.

Statistical analysis

Baseline characteristics were summarized using medians and interquartile ranges [25th-75th percentile] for continuous variables and percentages and counts for categorical variables. To compare changes in TMP, AP and VP between group S and T, multivariate linear regression analyses were conducted using objective, group-specific and time variables (at the start, at one hour, at two hours, at the end) and their cross-product term (interaction) as explanatory variables. Covariates (age, sex, total volume of substitution fluid, anticoagulant, machine, hematocrit, use of FFP) were accounted for in the models. In all regression models, the Huber-White robust sandwich estimator of the variance-covariance matrix was used to account for the dependence on repeated measures because the dataset contained repeated measurements in a single patient. For comparison of IgG and IgM isoagglutinin titers, multivariate proportional-odds logistic regression models were used, similarly to the above linear regression models. All statistical analyses were conducted with a two-sided significance level of 5%, except for interaction terms. Because of the underpowered nature of the interaction analysis, we used a 20% significance level for hypothesis testing of the interaction terms[32]. All analyses were performed using R ver. 3.6.3 (<https://www.r-project.org/foundation/>) with the “rms” and “RcmdrPlugin.EZR” packages.

Results

Characteristics of the Study Subjects (Table 1)

Demographic and baseline clinical data for each KTRs are shown in Table 1. A total of 58 sessions of SePE were performed in 30 KTRs, including SePE monotherapy (n=20) and tandem therapy (n=38). There were no cases of antibody-mediated rejection after transplantation.

Background data for each treatment mode (Table 2)

Background data for each group are shown in Table 2. Group T had a significantly higher prevalence of use of 5% albumin+FFP substitution fluid. There were no other significant differences between groups S and T.

Comparison of time changes of circuit internal pressure values (Table 3, Figs. 2-3)

There were significant differences in time changes of TMP and AP in group T compared to group S (P for interaction = 0.023 and 0.138, respectively, Figs. 2 and 3). There were no significant differences in time changes of VP in group T compared to group S (P for interaction = 0.265). Membrane exchange was required in two sessions in group T and one in group S due to TMP elevation and/or coagulation.

Comparison of decreases in anti-blood type antibody titers (Figs. 4)

There was a more significant decrease of IgG isoagglutinin titers after SePE in group T compared to group S (P for interaction = 0.182, Fig. 4). There was no significant difference in IgM isoagglutinin titers between groups T and S (P for interaction = 0.409).

Discussion/Conclusion

In this study, we investigated the safety and efficacy of tandem HD and SePE. The SePE circuit was connected in parallel with the HD circuit, and tandem HD and SePE therapy was performed using filtration methods (Figure 1). SePE sessions were divided into those using SePE monotherapy and those with tandem therapy. The internal pressures (AP and VP) were higher in tandem therapy, and there were significant differences in time changes of TMP and AP in between the session types. Moreover, there was a more significant decrease of IgG isoagglutinin titers in tandem therapy. The internal pressures were higher and TMP tended to increase more in tandem therapy compared to monotherapy, but we were able to perform the two treatments without any functional problems, and tandem therapy was effective in decreasing isoagglutinin titers.

Tandem HD and PE therapy has been extensively studied, but a definitive method has yet to be established[19-29]. Two techniques are generally used for separating plasma, centrifugation and filtration, but there are regional differences in their use[26]. In North America, most centers use centrifugation, but in Europe and Asia, filtration-based PE is more common[26]. The main advantage of filtration is the smaller extracorporeal volume compared to centrifugation, which is beneficial for tandem therapy with HD[26]. It is also advantageous for Asian patients who have a smaller physique. Taking this into consideration, we also perform SePE using filtration (Figure 1), and we have previously reported that the volume used for priming the circuit was about 370 mL in SePE (and about 320 mL in PE) [17].

In tandem HD and SePE, there are generally two ways to connect the circuits, in series and in parallel, with numerous variations for both methods and no definitive method[19-29]. We used the same method as Siami et al.[19] and Mahmood et al.[22], in which blood after a SePE session is returned to the patient through the dialyzer, which is advantageous because of

removal of sodium citrate contained in the substitution fluid and electrolyte correction when FFP is used. In addition, it is easier to connect and disconnect the circuits after each session or if problems such as SePE circuit coagulation occur. On the other hand, because branching into the HD and SePE circuits is required after blood removal, good vascular access is needed to obtain sufficient blood flow.

The Evacure Plus EC-4A10 (Kawasumi Laboratories), which we use as a plasma separator, has a smaller pore size, and TMP tends to increase more compared to conventional PE. However, because there is a lower risk for hemolysis due to the small pore diameter, the manufacturer alarm system is set at a high TMP of 150 mmHg. Since the sieving coefficient may change with time at a TMP of 60 to 70 mmHg or more, attention is required when TMP is high[12]. Therefore, we perform SePE at a TMP of ≤ 100 mmHg. In our patients, TMP and AP tended to increase more over time in tandem therapy, but both remained within the acceptable range and there were no functional problems in performing SePE (Table 2, Figures 2, 3). The internal pressures increase in tandem therapy because the apheresis circuit is connected to the arterial chamber of the dialysis circuit, so the range of the pressure alarm system needs to be reset.

Our results also showed that the decrease in IgG isoagglutinin titers was slightly better in tandem therapy compared to monotherapy. Because fluid is removed by HD in tandem therapy, the concentrated blood may affect removal of antibodies. However, the detailed mechanism is not clear. This point needs to be clarified using a further well-designed study.

This study has some limitations. First, because the sample size was small, it is possible that the background factors were not sufficiently adjusted, and a further study with a larger sample size is needed to confirm the results. Second, there are many variations in methods to connect the circuits in tandem therapy, and a comparison of these methods may be necessary. Third, a comparison with tandem HD and PE therapy is also required.

In conclusion, our results showed that tandem therapy with HD and SePE has no functional problems and is effective in decreasing isoagglutinin titers, although circuit internal pressures need to be monitored. This approach can also shorten the treatment time and alleviate the stress of punctures. These findings suggest that tandem HD and SePE therapy may be a beneficial treatment modality for apheresis before ABOi kidney transplantation.

Statements

Acknowledgement

Not applicable.

Statement of Ehtics

This study protocol was conducted in accordance with the Principles of the Declaration of Helsinki and the Declaration of Istanbul, and was approved by the ethics committee of Osaka City University Graduate School of Medicine (No. 4009). Opt-out consent was obtained instead of written informed consent; i.e., patients were provided with information explaining the proposed project (purpose, required individual data, and duration of the study) by means of an information sheet or hospital website and were given the opportunity to opt out.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

A.H. (first author) and T.N. (corresponding author) contributed to the concept, design, data acquisition, interpretation, and writing of the manuscript. D.K., D.M. and A.S. contributed to data analysis and interpretation. Y.T. and U.J. reviewed and revised the manuscript. All authors read and approved the final manuscript.

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Figure Legends

Figure 1: Selective plasma exchange circuit with hemodialysis[17]

Figure 2: Comparison of time changes of transmembrane pressure (TMP)

Figure 3: Comparison of time changes of arterial pressure (AP)

Figure 4: Distribution of decrease in IgG antibody titers.

ln Odds, natural logarithm transformed odds

Table 1. Characteristics of the Study Subjects

Case	Order and Frequency of Apheresis Therapy	Tandem HD and SePE therapy	SEX/Age	Blood type	HLA mismatch (antigen)	Dialysis duration (months)	DM	Anti-A/B IgG titers	Anti-A/B IgM titers
								Base	Base
1	DFPPx1 ⇒ SePE(A)x6	NO	M/67	AB+ ⇒ O+	4	0	0	256/256	16/16
2	SePE(A)x2 ⇒ PE x 6	YES	F/60	B+ ⇒ O+	5	131	0	1024	512
3	DFPPx1 ⇒ PE x 1 ⇒ SePE(A) x 1	YES	F/64	A+ ⇒ B+	4	130	1	16	16
4	DFPPx 1 ⇒ SePE(A) x 1	YES	F/32	AB+ ⇒ B+	1	4	0	8	8
5	DFPPx1 ⇒ PEx1 ⇒ DFPPx1 ⇒ SePE(A)x1	YES	F/39	B+ ⇒ O+	3	9	0	256	32
6	DFPPx2 ⇒ SePE(A)x1	NO	M/44	B+ ⇒ O+	3	40	0	64	32
7	DFPPx2 ⇒ SePE(A)x1	NO	F/69	AB+ ⇒ B+	3	10	1	16	16
8	DFPPx2 ⇒ SePE(F)x1	YES	F/68	B+ ⇒ A+	4	99	0	32	32
9	DFPPx2 ⇒ SePE(F)x1	YES	F/34	B+ ⇒ A+	2	23	1	8	8
10	DFPPx2 ⇒ SePE(F)x1	YES	M/66	B+ ⇒ A+	6	59	0	64	16
11	SePE(F)x1 ⇒ DFPPx1 ⇒ SePE(F)x1 ⇒ DFPPx1 ⇒ SePE(A)x1	YES	M/65	AB+ ⇒ A+	4	55	1	32	128
12	DFPPx1 ⇒ SePE(F)x1	YES	M/63	AB+ ⇒ A+	2	71	1	4	8
13	DFPPx1 ⇒ SePE(F)x1	YES	M/52	B+ ⇒ A+	4	24	1	16	16
14	SePE(A)x1 ⇒ SePE(F)x1	NO	M/70	A+ ⇒ B+	5	0	0	16	16
15	DFPPx1 ⇒ SePE(F)x2	YES	M/66	B+ ⇒ A+	3	1	1	256	256
16	SePE(A)x2	YES	F/44	B+ ⇒ A+	3	10	0	1	2
17	SePE(A)x2	YES	M/52	B+ ⇒ A+	5	16	1	4	4
18	SePE(A)x2	YES	M/53	B+ ⇒ A+	5	1	1	8	4
19	SePE(A)x2	YES	M/53	B+ ⇒ A+	2	9	0	8	4
20	SePE(A)x2	YES	M/53	B+ ⇒ A+	3	27	0	2	2
21	PEx1, SePE(A)x3	NO	M/51	A+ ⇒ B+	4	135	1	32	32
22	SePE(F)x2	YES	M/47	A+ ⇒ B+	3	18	0	16	8
23	SePE(A)x2	NO	M/37	AB+ ⇒ B+	2	0	1	16	8
24	SePE(A)x1	NO	M/53	B+ ⇒ O+	0	42	1	16	16
25	SePE(A)x2	YES	M/31	AB+ ⇒ B+	3	36	1	16	16
26	SePE(A)x1	NO	M/49	AB + ⇒ B +	5	0	1	2	1
27	SePE(A)x2	YES	M/65	AB + ⇒ A +	3	27	0	8	16
28	SePE(A)x3	NO	M/62	B + ⇒ A +	3	65	0	32	32
29	SePE(A)x1 ⇒ PEx1 ⇒ SePE(A)x1 ⇒ SePE(F)x1	YES	M/25	A + ⇒ O +	3	0	0	64	32
30	SePE(F)x1 ⇒ SePE(A)x1 ⇒ SePE(F)x2	YES	M/54	B+ ⇒ O+	4	14	0	256	16

SePE (A), selective plasma exchange using 5% albumin solution as the substitution fluid; SePE (F), selective plasma exchange partially using fresh frozen plasma as the substitution fluid;

DFPP, double-filtration plasmapheresis; PE, simple plasma exchange; SePE, selective plasma exchange; HD, hemodialysis; M, male; F, female; HLA, human leukocyte antigen; DM, diabetes

mellitus; IgG, immunoglobulin G; IgM, immunoglobulin M.

Table 2. Background data for each treatment mode^a

Factor	Group	Treatment mode (session)		P-value
		Single (n=20)	Tandem (n=38)	
Anticoagulant: n (%)	Heparin	12 (60.0)	28 (73.7)	0.373
	Nafamostat mesilate	8 (40.0)	10 (26.3)	
Machine: n (%)	ACH-Σ	1 (5.0)	9 (23.7)	0.172
	KM-9000	6 (30.0)	12 (31.6)	
	TR-55X	13 (65.0)	17 (44.7)	
Substitution fluid: n (%)	5% Albumin	19 (95.0)	23 (60.5)	0.005
	5% Albumin+FFP	1 (5.0)	15 (39.5)	
Total volume of substitution fluid (ml)		5795 [5428, 6115]	5915 [5393, 6260]	0.719
Hematocrit (%)		31.4 [31.2, 36.1]	34.7 [31.3, 37.9]	0.096
Pre-IgG isoagglutinin titers (fold)		16 [8, 128]	8 [4, 32]	0.05
Pre-IgM isoagglutinin titers (fold)		8 [4, 16]	4 [2, 8]	0.134

^aValues are expressed as the median [IQR] or number (percentage).

Table 3. Comparison of time changes of circuit internal pressure values^a

	Treatment mode	At the start	At 1h	At 2h	At the end	P for interaction
Transmembrane pressure (mmHg)	Single	32 [28, 36]	38 [33, 47]	39 [36, 49]	44 [36, 56]	0.023
	Tandem	33 [25, 44]	42 [36, 58]	48 [38, 60]	52 [41, 70]	
Arterial pressure (mmHg)	Single	108 [96, 115]	104 [95, 121]	102 [91, 111]	102 [98, 103]	0.138
	Tandem	275 [251, 289]	283 [245, 307]	268 [245, 302]	264 [250, 302]	
Venous pressure (mmHg)	Single	64 [56, 68]	65 [56, 74]	62 [55, 66]	64 [52, 65]	0.265
	Tandem	231 [208, 247]	238 [207, 245]	222 [204, 242]	228 [209, 242]	

^aValues are expressed as the median [IQR].

Supplemental Material

Immunosuppression protocol

Mycophenolate mofetil (MMF) 1 g/day (0.5 g/day for patients aged ≥ 65 years) was started 4 weeks before transplantation. All patients with titers $<1:512$ received a single dose of rituximab (150 mg/m^2) 2 weeks before transplantation. Patients with titers $\geq 1:512$ and those with rebound titers received rituximab (150 mg/m^2) 2 weeks before and on the day of transplantation. A calcineurin inhibitor (tacrolimus or cyclosporine initiated 3 days prior to transplantation), MMF or everolimus, steroids, and basiliximab were used for post-transplant immunosuppression.

Conditions for SePE

Apheresis was performed using a KM-9000 (Sanyo Electronic Industries Co., Ltd. Okayama, Japan) or TR55X (Toray Medical Co., Ltd. Tokyo, Japan) or ACH- Σ (Plasauto Σ in overseas models) (Asahikasei Medical Co., Ltd. Tokyo, Japan) blood purification system. SePE was performed using the Evacure Plus EC-4A10 (Kawasumi Laboratories Inc., Tokyo, Japan; sieving coefficients: albumin; 0.61, IgG; 0.44, fibrinogen; 0) as the plasma separator. During SePE, blood flow was maintained at 100 ml/min with a plasma separation rate of 30 ml/min, and unfractionated heparin or nafamostat mesilate was used as the anticoagulant. Plasma volume (PV) was calculated as: $PV = (BW/13) \times (100 - Ht)/100$, where BW and Ht indicate body weight (kg) and hematocrit (%), respectively. The target processed PV was set at 2 PV. In tandem HD and SePE, SePE was performed in parallel with the HD circuit, with a blood flow rate of 100 mL/min into the SePE circuit. To prevent a decrease in blood pressure due to the difference in colloid osmotic pressure between the plasma and substitution fluid, a Crit-

Line monitor was connected to the blood circuit, and the intravascular blood volume was monitored.

Measurement of clinical data

Isoagglutinin titers were measured by a tube centrifugation test, anti-A/B IgM titers were determined using the saline agglutination technique, and IgG titers were evaluated using an indirect Coombs' test. Changes in isoagglutinin titers and serum IgG, IgM, fibrinogen and factor XIII levels were examined, in addition to any adverse effects.