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Increasing use of therapeutic apheresis as a liver-saving modality☆

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ABSTRACT

Introduction: Therapeutic plasma exchange (TPE) is used for temporary support of liver function in patients presenting with early graft dysfunction after liver transplantation (LT) or liver surgery. We analyzed the effect of therapeutic apheresis on patients with liver disease.
Methods: Between January 2011 and August 2016, 93 apheresis procedures were performed for 26 patients at our institution. Anti-ABO isoagglutination immunoglobulin (Ig) M titer was checked using a type A and type B 3% red blood cell (RBC) suspension in saline with two-fold serial dilutions of patient serum. Anti-ABO isoagglutination IgG titer was checked by a type A and B 0.8% RBC suspension using a low-ionic strength/Coombs card.
Results: ABO-incompatible (ABOi) LT was the most common ($n = 10$, 38.5%) indication for apheresis; early graft dysfunction after LT ($n = 8$, 30.7%) was the second most common. Median initial IgM and IgG anti-ABO titers for ABOi LT recipients were 1:16 (range, 1:8–1:128) and 1:48 (range, 1:8–1:2048). We performed preoperative TPE in 10 recipients (median number of sessions, 1.5; range, 1–11). Among patients with early graft dysfunction, those who underwent living donor LT had better survival (4/4; 100%) than those who underwent nonliving donor LT (0/3; 0%). Patients who underwent living donor LT first and then additional LT also survived after three TPE sessions.
Conclusion: Therapeutic apheresis is associated with a good survival rate and is essential for liver support in patients with early graft dysfunction after LT or posthepatectomy liver failure and during preparation for ABOi LT.

1. Introduction

Therapeutic plasma exchange (TPE) can be used for temporary support of liver function in patients undergoing early graft dysfunction after liver transplantation (LT) [1,2]. However, the use of TPE in patients with early graft dysfunction is off-label as an adjunct therapy due to the lack of guidelines. Most reliable guidelines regarding the use of therapeutic apheresis in clinical practice have been issued and updated by the American Society for Apheresis (ASFA) [3]. Guidelines of the ASFA do not include use in patients with early graft dysfunction. Even though TPE is effective for patients with early graft dysfunction, there are no consensus regarding the process of performing TPE. In this retrospective clinical study, we analyzed the efficacy of therapeutic apheresis for patients with liver disease.

2. Materials and methods

Between January 2011 and August 2016, 93 TPE procedures were performed for 26 patients in the hepatology department at a single hospital in the Republic of Korea. During the study period, a total of 320 LTs were performed at our hospital. Clinical information including age, sex, diagnosis, and laboratory data were assessed through a retrospective chart review. Venous access was obtained through large-bore (15–17 gauge) surgically implanted tunneled catheters in the internal jugular vein or via temporary dual-lumen catheters placed in the femoral or internal jugular vein. Procedures were performed using an apheresis device (Com.Tec; Fresenius Kabi, Bad Homburg, Germany). Anticoagulant citrate dextrose

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Table 1
Indications for plasmapheresis and demographic details of the patients.

Diagnosis	Patients, *N*	Sex (F/M)	Median age (range)	TPE, *N*
ABO-incompatible liver transplantation	10	0/10	58 (51–71)	38
Early graft dysfunction	8	4/4	52 (40–62)	28
Hepatic failure	4	2/2	58 (41–74)	5
Posthepatectomy liver failure	3	1/2	64 (60–67)	16
Acute rejection of liver transplantation	1	0/1	50	6

F, female; M, male; TPE, therapeutic plasma exchange.

solution A (ACD-A; 12:1) with 5% albumin and fresh-frozen plasma (FFP; 14:1) were used for anticoagulation. The substitution fluids most often used by our unit were 5% albumin solution plus FFP or FFP alone.

The anti-ABO isoagglutination IgM titer was checked by using a type A and type B 3% red blood cell (RBC) suspension (Ortho Clinical Diagnostics, Pencoed, UK) in saline with two-fold serial dilutions of patient serum at room temperature, followed by centrifugation and scoring for agglutination. The anti-ABO isoagglutination IgG titer was checked using a type A and type B 0.8% RBC suspension (Ortho Clinical Diagnostics) using a low-ionic strength/Coombs card (Biorad, Murten, Switzerland) with two-fold serial dilutions of patient serum. The anti-ABO IgM/IgG titer was monitored every day starting from TPE until 2 weeks after LT. To reduce anti-ABO isoagglutination, a single dose of rituximab (300 mg/m^2/body surface area) was administered to all patients 2–3 weeks before LT. After 1 week of injections of rituximab, isoagglutination titration was monitored every day. If the IgG titer was higher than 1:256, then TPE was started on day 7 after injection of rituximab and TPE was performed every other day. If the IgG titer was lower than 1:256, then TPE was started on day 14 after rituximab injection.

When hyperbilirubinemia (>10 mg/dL) occurs in patients with early graft dysfunction, the physician requests TPE. TPE was performed every other day until the bilirubin level was <10 mg/dL. For patients with other diseases, we performed TPE when requested by the physician for patients with hyperbilirubinemia (>10 mg/dL), and the schedule was the same as for early graft dysfunction.

The association between characteristics of recipients of ABO-incompatible (ABOi) LT and the amount of TPE was assessed using Fisher's exact tests and Mann–Whitney *U*-test. Statistical tests were performed using SPSS version 22.0 software (SPSS, Inc., Chicago, IL). Results were considered statistically significant for $P < 0.05$.

This research was approved after full committee review by the Institutional Review Board at Pusan National University Yangsan Hospital (no. 05-2015-106).

3. Results

Indications for TPE in our hepatology department are listed in Table 1. ABOi LT was the most common indication ($n = 10$; 38.5%), and early graft dysfunction after LT ($n = 8$; 30.7%) was the second most common indication. ABOi LT has been performed since 2015 and its use has increased rapidly.

From February 2015 to August 2016, 10 recipients planned to undergo ABOi LT. Nine patients (90%) had hepatitis B virus-induced liver cirrhosis; among them, eight patients had hepatocellular carcinoma. The median initial IgM and IgG anti-ABO titers were 1:16 (range, 1:8–1:128) and 1:48 (range, 1:8–1:2048), respectively. We performed preoperative TPE for 10 recipients (median number of sessions, 1.5; range, 1–11). Results of patients who received fewer than five TPE sessions were compared with those of patients who received more than five sessions, (Table 2). The initial anti-ABO IgM titer was significantly different and patients with type O blood received more TPE sessions than patients with non-O blood types. After surgery, one patient (10%) received TPE. One death occurred as a result of multi-organ failure during TPE before transplantation. There was one case of acute rejection (10%) that was treated successfully with immunosuppressants. There were two cases of biliary anastomotic stricture (20%). Antibody-mediated rejection and graft failure did not occur.

Early graft dysfunction occurred after LT in 2.4% (8/320) of all LT patients at our hospital. However, more than half of these patients ($n = 5$; 62.5%) survived with the use of TPE (Table 3). We performed TPE for 11 patients with either early graft dysfunction after LT or major hepatectomy. A median of three (range, 2–8) TPE sessions was performed. Among patients with early graft dysfunction, patients who underwent living donor LT had better survival rates (4/4; 100%) than those who underwent nonliving donor LT (0/3; 0%). A patient who underwent living donor LT first and then another LT also survived after three TPE sessions. One patient (case 5) had persistently elevated bilirubin after five TPE sessions.

Table 4 shows the etiology and demographics for hepatic failure patients, who received TPE. The median number of TPE sessions was one. Three patients died due to underlying disease; one patient died after acute graft rejection and six sessions of TPE. One patient was transferred to an outside hospital for LT.

4. Discussion

TPE removes toxic substances, including plasma bilirubin, and corrects coagulopathy by repletion of coagulation factors in plasma. TPE can be used as a bridging therapy while a donor liver is

Table 2
Baseline characteristics of recipients of ABO incompatible liver transplantation.

	Total	TPE < 5	TPE > 5	*P*-value	
				Univariate	Multivariate
Age	58 (50–71)	61 (54–71)	55 (50–57)	0.125	0.707
Sex (F/M)	0/10	0/7	0/3		
Admission duration	37 (24–138)	31 (24–84)	49 (24–138)	0.269	0.021
Inital anti-ABO IgM titer	1:16 (1:8–1:128)	1:16 (1:8–1:64)	1:128 (1:16–1:128)	0.079	0.05
Initial anti-ABO IgG titer	1:48 (1:16–1:2048)	1:16 (1:8–1:64)	1:512 (1:256–1:2048)	0.013	0.008
Anti-ABO IgG titer after 1 week of rituximab treatment	1:32 (1:2–1:1024)	1:16 (1:2–1:64)	1:512 (1:62–1:1024)	0.016	0.015
Anti-ABO IgM titer after 1 week of rituximab treatment	1:12 (1:1–1:128)	1:8 (1:1–1:64)	1:64 (1:16–1:128)	0.064	0.067
ABO type O/non-O	7/3	0/7	2/1	0.067	0.003

F, female; M, male; TPE, total plasma exchange.