Adjuvant Therapeutic Plasma Exchange in Liver Failure

Assessments of Clinical and Laboratory Parameters

Mehmet Bektas, MD, Ramazan Idilman, MD,* Irfan Soykan, MD,* Ender Soydan, MD,† Mutlu Arat, MD,† Kubilay Cinar, MD,* Sahin Coban, MD,* Ali Tuzun, MD,* Hakan Bozkaya, MD,* Necati Ormeci, MD,* and Ali Ozden, MD**

Background: Therapeutic plasma exchange (TPE) seems to be an effective approach for clearing toxins, immune-mediated antigens, and other particles from the circulation. The aim of this study was to analyze the positive effects of TPE on clinical and biochemical parameters of liver failure.

Patients and Methods: Between January 2001 and March 31, 2005 individuals (men/women, 17/14; median age, 42.7 ± 15.8 y) with acute and chronic liver failure who underwent a total of 113 TPEs (median session 3.7) were retrospectively reviewed. TPE was performed using the Fresenius AS-TEC 204 cell separator (Fresenius AG, Germany). The indication for TPE was severe coagulopathy (prothrombin time > 20 s), severe hepatic encephalopathy, hyperbilirubinemia, and candidacy for liver transplantation. All patients were examined before and immediately after the last TPE session.

Results: When compared with baseline, there was significant improvement in hepatic encephalopathy stage (from median score 3.0 to 1.0, $P = 0.001$), serum prothrombin time (from median 26.0 to 20.0 s, $P = 0.003$), aminotransferases ($P < 0.001$), and total bilirubin levels (from median 35.0 to 23.3 mg/dL, $P < 0.001$) after TPE. Thirteen of the thirty-one individuals (41.9%) died in the hospital. The mean follow-up period of 18 survival patients was 35.9 ± 5.6 months and 10 of those survived (55.6%, 10/18). No serious adverse effect of TPE was observed in any of the patients during or after completion of TPE. Only 6 patients experienced minor transfusion reactions.

Conclusions: TPE seems to be effective in improving hepatic encephalopathy stage and liver tests in individuals with acute and chronic liver failure. The data suggest that TPE is safe and tolerable in such individuals, however, overall survival remains poor despite TPE.

Received for publication November 2, 2006; accepted August 15, 2007.
From the Departments of *Gastroenterology; and †Hematology, Ankara University School of Medicine, Ankara, Turkey.
The authors declare no conflict of interest.
Ramazan Idilman and Mutlu Arat have been supported by the Turkish Academy of Sciences, in the framework of the Young Scientist Award Program (EA-TUBA-GEBIP/2001-1-1, 2004-1-1).
Reprints: Ramazan Idilman, MD, Department of Gastroenterology, Ankara University School of Medicine, Ibn-i Sina Hospital, Sihhiye, Ankara, Turkey 06100 (e-mail: idilman@dialup.ankara.edu.tr).

Key Words: therapeutic plasma exchange, liver failure, liver assist device

(*J Clin Gastroenterol* 2008;42:517–521)

The management of liver failure remains a challenge for physicians. Despite great improvements in the field of liver transplantation, many individuals with liver failure die while awaiting transplantation because of its various limitations, including organ shortage and its significant morbidity and mortality.[1–4] In addition, some individuals with liver failure may not be eligible candidates for liver transplantation because of underlying medical, technical, or other problems.[1–4]

In recent years, there has been considerable interest in the use of newer forms of biologic and nonbiologic liver support that may provide a bridge until spontaneous recovery of the native liver occurs or until an appropriate donor is available.[5–11] However, the widespread clinical applicability of these new approaches has yet to be defined.

Therapeutic plasma exchange (TPE) seems to be an effective approach for clearing toxins, immune-mediated antigens, and other particles from the circulation.[6–8,12–14] With TPE, liver toxic substances and potentially harmful inflammatory mediators are removed from the circulation and replaced with donor plasma.[6–8,12] Although TPE has been used previously in the management of individuals with drug-induced liver failure, no clear data on the efficiency of TPE in liver failure are available in the literature. The aim of this study was to analyze the positive effects of TPE on clinical and biochemical parameters in both acute and chronic liver failure.

MATERIALS AND METHODS

Patients

Between January 2001 and March 2005, 31 individuals [men/women, 17/14; mean age, 42.7 ± 15.8 y (range, 13 to 77 y) with liver failure who underwent a total of 113 TPEs (median 3.7; range, 1 to 12) were retrospectively reviewed. The primary etiologies of liver failure were hepatitis B virus-induced cirrhosis in 3 patients, delta virus-induced cirrhosis in 1 patient, hepatitis C virus-induced cirrhosis in 1 patient,

TABLE 1. Etiologies of Liver Failure in Individuals Who Underwent TPE

	Etiologies	n
Group 1		
Fulminant liver failure	Hepatitis B virus-induced	4
	Hepatitis A virus-induced	1
	Cryptogenic	1
	Total	6
Drug-induced severe hepatitis	Total	10
Group 2		
Cirrhosis	Hepatitis B virus-induced	3
	Hepatitis D virus-induced	1
	Hepatitis C virus-induced	1
	Ethanol-induced cirrhosis	3
	Biliary cirrhosis	3
	Wilson disease	2
	Cryptogenic	2
	Total	15
	Overall	31

ethanol-induced cirrhosis in 3 patients, biliary cirrhosis in 3 patients, Wilson disease in 2 patients, cryptogenic cirrhosis in 2 patients, drug-induced severe hepatitis in 10 patients, and acute fulminant liver failure (ALF) in 6 patients (Table 1). Patients were divided into 2 distinct groups. Group 1 (n = 16) consisted of those diagnosed with drug-induced severe hepatitis and ALF, whereas group 2 (n = 15) consisted of those diagnosed with chronic liver failure (Table 1). The indication for TPE was severe coagulopathy [prothrombin time (PT) > 20 s], grade 3 to 4 hepatic encephalopathy, hyperbilirubinemia with/without abnormal renal function, and candidacy for liver transplantation. All individuals signed an informed consent before each procedure.

Methods

TPE Procedure

TPE was performed using the Fresenius AS-TEC 204 cell separator (Fresenius AG, Germany) mostly via central venous catheter as previously described.[15] In a typical TPE procedure an average of 1:1 or 1.5:1 of the patient's plasma volume is exchanged by continuous flow apheresis technique. Both human albumin (5%) and fresh frozen plasma were used as replacement fluid. The median exchange volume per procedure is 2864 mL (range, 1500 to 3750 mL). TPE treatment was planned as 2 consecutive days for the first cycle and was continued on a thrice-weekly basis until either clinical or biochemical response was achieved, the patient expired or the patient was transplanted. The procedure was ceased in patients not responding.

Definitions

ALF was defined according to the O'Grady criteria.[16,17]

All patients were examined by the same physician (M.B.), before and immediately after TPE. Neurologic status was determined by clinical assessment using a standard hepatic encephalopathy scale.[18] Biochemical parameters were analyzed 2 hours after TPE.

Follow-up

All surviving patients were seen at the fourth week and at monthly intervals thereafter in the Outpatient Clinic. Vital signs and physical examination were assessed. Blood was drawn for evaluation of biochemical parameters during the follow-up period.

Statistical Analysis

All patients were included. The data were summarized as mean ± SD for normal and median (range) for non-normal variables and as percentages for counts. Differences between Recovery and Deceased groups were tested by Student t test for normal and Mann-Whitney for non-normal variables, and χ^2 test and Fisher exact test for counts. Wilcoxon test was used to analyze premeasurement and postmeasurement tests. A P value of < 0.05 was considered to be significant.

RESULTS

Clinical and biochemical parameters before and after TPE are shown in Table 2.

Neurologic Status

At the initiation of TPE, 15 patients had stage 3 or 4 encephalopathy. When compared with baseline, neurologic examination findings after TPE were significantly improved, from median score 3.0 (range, 0 to 4) to 1.0 (range, 0 to 3) ($P = 0.001$) (Table 2). This improvement was mostly observed after the first TPE session.

Correction of Coagulopathy

A significant improvement in terms of the serum PT level after TPE was observed [from median 26.0 s (range, 12.6 to 61.0 s) to 20.0 s (range, 12.8 to 38.0 s), $P = 0.003$].

Of note, the median platelet counts improved after TPE from 108.0×10^3 U/L (range, 28 to 1041×10^3 U/L) to 120.0×10^3 U/L (range, 10 to 650×10^3 U/L) ($P = 0.021$).

Liver Function

TPE improved the abnormal liver tests. When compared with baseline, serum aminotransferases levels had significantly decreased after TPE [median serum aspartate aminotransferase level: from 172.5 IU/L (range, 39 to 4722 IU/L) to 108.0 IU/L (range, 23 to 375 IU/L) $P < 0.001$; serum alanine aminotransferase level: 124.5 IU/L (range, 17 to 3285 IU/L) to 58.5 IU/L (range, 13 to 486 IU/L), $P < 0.001$]. The median serum total bilirubin level decreased from 35.0 mg/dL (range, 1.7 to 68.0 mg/dL) to 23.3 mg/dL (range, 1.5 to 51.0 mg/dL) ($P < 0.001$). Of note, the median serum albumin level was increased after TPE [from 2.7 g/dL (range 2.0 to 3.6 g/dL) to 3.2 g/dL (range 2.4 to 4.0 g/dL), $P < 0.001$].

Renal Function

Before TPE, 18 patients had abnormal renal function (median serum creatinine level 1.8 mg/dL; range,

TABLE 2. Clinical and Biochemical Parameters Before and After Plasmapheresis

	All Individuals (N = 31)			Group 1 (N = 16)			Group 2 (N = 15)		
Median (Min-Max)	**Baseline**	**After TPE**	***P***	**Baseline**	**After TPE**	***P***	**Baseline TPE**	**After TPE**	***P***
Hepatic encephalopathy	3 (0-4)	1 (0-3)	0.001	3 (0-4)	0.5 (0-3)	0.01	3 (0-4)	1 (0-3)	0.02
Total bilirubin (N: 0.3-1.2 mg/dL)	35.0 (1.7-68.0)	23.3 (1.5-51.0)	< 0.001	32 (18.8-68)	17.2 (5.0-42.8)	< 0.001	38 (1.65-56.0)	31.4 (1.5-51)	0.009
Serum ALT level (N: 0-34 U/L)	124.5 (17-3285)	58.5 (13-486)	< 0.001	154 (22-3285)	56 (17-486)	0.005	84 (17-520)	61 (13-180)	0.016
Serum AST level (N: 0-31 U/L)	172.5 (39-4722)	108 (23-375)	< 0.001	184 (48-4722)	117 (46-375)	0.005	155 (39-890)	102 (23-230)	0.019
Serum creatinine level (N: 0.66-1.09 mg/dL)	1.8 (0.6-5.9)	1.4 (0.8-6.2)	0.236	1 (0.6-4.5)	1.3 (0.8-3.7)	0.388	2.25 (0.8-5.9)	1.75 (0.8-6.2)	0.507
Serum PT level	26 (12.6-61.0)	20 (12.8-38.0)	0.003	23.5 (17.0-61.0)	18.0 (12.8-35)	0.004	27.3 (12.6-48.0)	25 (14-38)	0.231
Serum albumin level (N: 3.5-5.2 g/dL)	2.7 (2.0-3.6)	3.2 (2.4-4.0)	< 0.001	2.9 (2.1-3.6)	3.5 (2.4-4)	0.111	2.5 (2.0-3.5)	3.1 (2.6-3.7)	0.009
Platelet count (N: 196-451 $\times 10^3$ U/L)	108 (28-1041)	120 (10-650)	0.021	212 (29-1041)	130 (33-650)	0.109	84 (28-375)	75 (10-256)	0.099

All values were given median (min-max).
ALT indicates alanine aminotransferase; AST, aspartate aminotransferase; N, normal.

0.6 to 5.9 mg/dL). Serum creatinine level slightly decreased after TPE, to 1.4 mg/dL (range, 0.8 to 6.2 mg/dL) ($P = 0.23$). Of these 18 patients, abnormal renal function persisted in 5.

Patient Outcome

Thirteen of the thirty-one individuals (41.9%) who underwent TPE died in the hospital within 30 days. Of these, 2 had ALF, 4 had drug-induced severe hepatitis, and 7 had chronic liver failure (Fig. 1). The mean follow-up period of the 18 surviving patients was 35.9 ± 5.6 months and 10 of those survived (55.6%, 10/18). Overall survival was 32.3% (10/31); 75.0% in individuals with ALF (3/4), 100% in drug-induced severe hepatitis (6/6), and 12.5% in chronic liver failure (1/8) (Fig. 1). Two of the four patients with ALF underwent successful living-related liver transplantation (one of them expired on posttransplant day 5 due to intracranial event), and the remaining 2 experienced spontaneous recovery).

Adverse Effects of TPE

No serious adverse effects, including hemodynamic instability, bleeding, electrolyte and acid-base abnormalities, systemic organ failure, or infection were observed during or after TPE. Six patients experienced nonhemolytic transfusion reactions including subfebrile fever and urticaria, which were controlled with symptomatic management.

DISCUSSION

The main goals of liver support systems are to improve the encephalopathy stage, abnormal coagulopathy, and complications of additional end organ damage in individuals with liver failure.[5,19,20] In the present study, we assessed the efficacy of TPE on clinical and biochemical parameters of 31 individuals with acute and chronic liver failure. Hepatic encephalopathy stage was significantly improved after TPE, as other investigators have reported.[12–14,19] This improvement was observed in both acute and chronic liver failure. It is indicated that TPE improves consciousness levels and tends to normalize hyperkinetic circulation due to removal of dialyzable neurotoxic substances from the systemic circulation.

TPE significantly improved the abnormal coagulation profile. In the present study, when compared with baseline, serum PT level was significantly improved after TPE. This result is comparable with that observed by Singer et al[12] who reported that TPE can correct the bleeding diathesis in children with ALF with the correction of coagulation profiles. Several factors can explain this correction: first, TPE seems to be an effective approach for clearing accumulated anticoagulant toxins from the circulation[12–14] and second, it is a result of replacement of clotting factors during TPE.

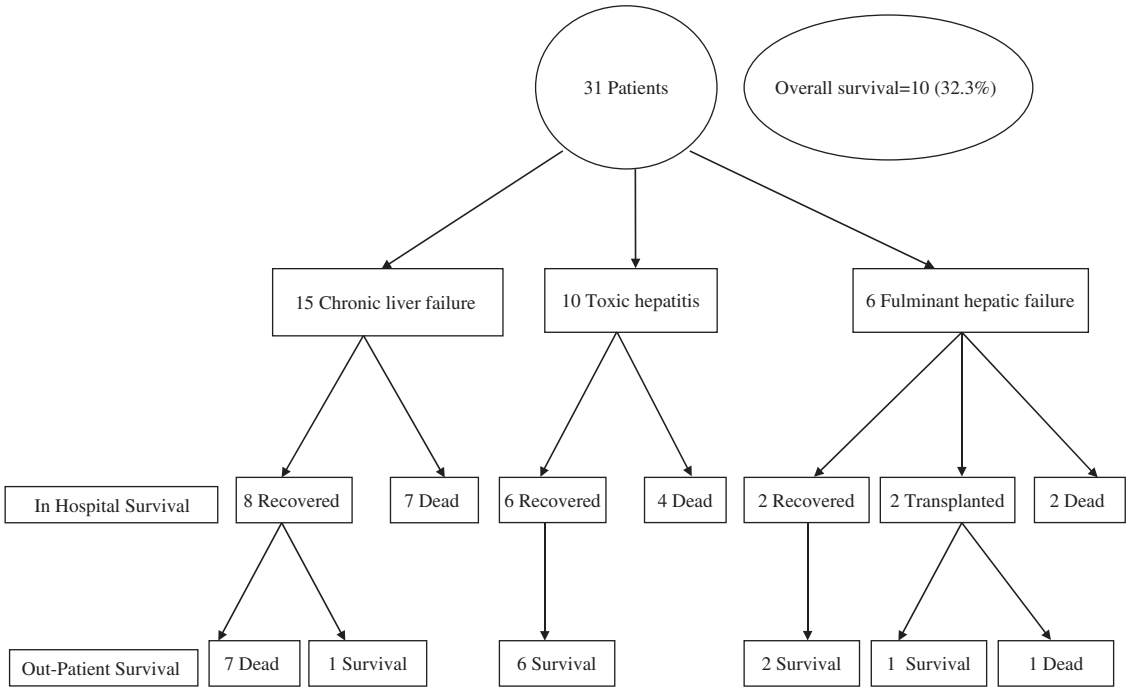

FIGURE 1. The outcome of patients with liver failure who underwent TPE.

The dilutional effect of plasmapheresis on decreasing the serum aminotransferases and bilirubin levels was well demonstrated by Singer et al.[12] In the present study, the initial serum aminotransferases and total bilirubin levels were significantly improved after TPE. Unfortunately, total bilirubin level could not be maintained within normal range after the completion of TPE indicating that TPE does not produce a real effect on liver enzymes and bilirubin levels.

Short-term survival of all patients involved in this study was 55.6%: 75.0% for individuals with ALF, 100% in drug-induced severe hepatitis, and 13.0% in chronic liver failure. The finding in ALF is comparable with that obtained by Freeman et al,[7] who reported a 55% survival in plasmapheresed cases with ALF. On the basis of the results of these studies, plasmapheresis seems to improve short-term survival in individuals with ALF and in drug-induced severe hepatitis.

TPE was well tolerated in all individuals. No serious adverse effects to treatment were observed in any of the patients during or after completion of TPE. Six patients had transfusion reactions, which were controlled with symptomatic management.

In conclusion, although TPE does not affect the natural course of the liver disease or promote liver regeneration, the present data suggest that TPE seems to be effective in improving hepatic encephalopathy stage, PT, and liver tests in individuals with liver failure and may allow a sufficient period for liver regeneration. The data suggest that TPE is safe and tolerable in such individuals; however, overall survival remains poor despite TPE.

REFERENCES

1. Bismuth H, Samuel D, Gugenheim J, et al. Emergency liver transplantation for fulminant hepatitis. *Ann Intern Med*. 1987;107:337–341.
2. Williams R, Gimson AE. An assessment of orthotopic liver transplantation in acute liver failure. *Hepatology*. 1984;4:22S–24S.
3. Bismuth H, Samuel D, Castaing D, et al. Liver transplantation in Europe for patients with acute liver failure. *Semin Liver Dis*. 1996;16:415–425.
4. Bismuth H, Samuel D, Castaing D, et al. Orthotopic liver transplantation in fulminant and subfulminant hepatitis. The Paul Brousse experience. *Ann Surg*. 1995;222:109–119.
5. van de Kerkhove MP, Hoekstra R, Chamuleau RAFM, et al. Clinical application of bioartificial liver support systems. *Ann Surg*. 2004;240:216–230.
6. Buckner CD, Clift RA, Volwiler W, et al. Plasma exchange in patients with fulminant hepatic failure. *Arch Intern Med*. 1973;132:487–492.
7. Freeman JG, Matthewson K, Record CO. Plasmapheresis in acute liver failure. *Int J Artif Organs*. 1986;9:433–438.
8. Kondrup J, Almdal T, Vilstrup H, et al. High volume plasma exchange in fulminant hepatic failure. *Int J Artif Organs*. 1992;15:669–676.
9. Yamazaki Z, Kanai F, Idezuki Y, et al. Extracorporeal methods of liver failure treatment. *Biomater Artif Cells Artif Organs*. 1987;15:667–675.
10. Catalina MV, Barrio J, Anaya F, et al. Hepatic and systemic haemodynamic changes after MARS in patients with acute on chronic liver failure. *Liver Int*. 2003;23:39–43.
11. Rıfai K, Ernst T, Kretschmer U, et al. Prometheus, a new extracorporeal system for the treatment of liver failure. *J Hepatol*. 2003;39:984–990.
12. Singer AL, Olthoff KM, Kim H, et al. Role of plasmapheresis in the management of acute hepatic failure in children. *Ann Surg*. 2001;234:418–424.
13. Larsen FS, Hansen BA, Jorgensen LG, et al. High volume plasmapheresis and acute liver transplantation in acute fulminant hepatic failure. *Transplant Proc*. 1994;26:1788.

14. Clemmesen JO, Kondrup J, Nielsen LB, et al. Effects of high-volume plasmapheresis on ammonia, urea and amino acids in patients with acute liver failure. *Am J Gastroenterol*. 2001;96: 1217–1223.
15. Arslan O, Arat M, Tek I, et al. Therapeutic plasma exchange in a single center: Ibn-I Sina experience. *Transfusion Apheresis Sci*. 2004; 30:181–184.
16. O'Grady JG, Schalm SW, Williams R. Acute liver failure: redefining the syndromes. *Lancet*. 1993;342:273–275.
17. Aladag M, Gurakar A, Jalil S, et al. A liver transplant center experience with liver dialysis in the management of patients with fulminant hepatic failure: a preliminary report. *Transplant Proc*. 2004;36:203–205.
18. Leevy CM. Clinical diagnosis, evaluation and treatment of liver disease in alcoholics. *Fed Proc*. 1967;26:1474–1481.
19. Clemmesen JO, Gerbes AL, Gulberg V, et al. Hepatic blood flow and splanchnic oxygen consumption in patients with liver failure. Effect of high volume plasmapheresis. *Hepatology*. 1999;29: 347–355.
20. Akdogan M, Camci C, Gurakar A, et al. The effect of total plasma exchange on fulminant hepatic failure. *J Clin Apheresis*. 2006;21: 96–99.

