Therapeutic Apheresis and Dialysis 11(5):391–395
doi: 10.1111/j.1744-9987.2007.00505.x

A Case Report of Hepatorenal Syndrome Treated With Plasma Diafiltration (Selective Plasma Filtration with Dialysis)

Hajime Nakae,[1] Toshiko Igarashi,[1] Kimitaka Tajimi,[1] Tomoyuki Kusano,[2] Satoshi Shibata,[2] Makoto Kume,[2] Tsutomu Sato,[2] and Yuzo Yamamoto[2]

[1]Department of Integrated Medicine, Division of Emergency and Critical Care Medicine, and [2]Department of Gastroenterological Surgery, Akita University School of Medicine, Akita, Japan

Abstract: Plasma diafiltration (PDF) (selective plasma filtration with dialysis) is blood purification therapy in which simple plasma exchange is performed using a membrane plasma separator (Evacure EC-2A) while dialysate flows outside of the hollow-fibers. A 74-year old man with hepatorenal syndrome underwent four sessions of PDF and three sessions of HDF. Finally he recovered from hepatorenal syndrome. In this therapy, the levels of total bilirubin, interleukin-18, creatinine, and cystatin C were significantly reduced. On the other hand, there were no significant differences in the total protein and albumin levels before and after PDF. PDF may be one of the most useful blood purification therapies for hepatorenal syndrome in terms of medical economics. **Key Words:** Hepatorenal syndrome, Plasma diafiltration, Plasma exchange.

Blood purification therapy with plasma exchange (PE) alone for the treatment of acute liver failure involves citrate intoxication associated with large doses of fresh frozen plasma (FFP) (1). We previously reported the usefulness of combination therapy with continuous hemodiafiltration (CHDF), by which electrolyte imbalance is corrected and water is controlled simultaneously (2–6). PE + CHDF therapy, however, still involves unknown infection and economic problems, because 40–50 units of FFP are used. In addition, this therapy requires many circuits because two columns and two consoles are used, and thus the risk of infection associated with attachment or detachment of the circuits cannot be completely eliminated. Plasma diafiltration (PDF) (selective plasma filtration with dialysis) is a blood purification therapy in which simple PE is performed using a membrane plasma separator while dialysate flows outside of the hollow-fibers. PDF, using about half the dose of FFP required by conventional PE, may achieve results similar to those of conventional PE (7). Here, we report on a patient who underwent PDF for the treatment of hepatorenal syndrome.

Received September 2006.
Address correspondence and reprint requests to Dr Hajime Nakae, Department of Integrated Medicine, Division of Emergency and Critical Care Medicine, Akita University School of Medicine, 1-1-1 Hondo, Akita 010-8543, Japan. Email: nakaeh@doc.med.akita-u.ac.jp
Presented in part at the 26th Annual Meeting of the Japanese Society for Apheresis held 28–29 July 2006 in Otsu, Japan.

CASE REPORT

A 74-year-old man with bile duct cancer was admitted to our hospital in October 2005 for surgery. Before surgery, cholangitis developed after endoscopic retrograde cholangiopancreatography (ERCP), and he underwent percutaneous transhepatic biliary drainage (PTBD). In November, he underwent left hepatic lobectomy and bile duct resection. Because atrial fibrillation (AF) persisted postoperatively, heparin was infused. On postoperative day 16, the patient had massive bleeding from the drain near the anastomotic site. Immediate coil embolization of the hepatic aorta was performed, but the patient showed subsequent repeated episodes of pyrexia (38–39°C). Methicillin-resistant *Staphylococcus aureus* (MRSA) was detected in the drain in December. Because urine output decreased on

TABLE 1. *Laboratory data on admission of ICU*

Hematology		Biochemistry	
WBC	5300 mm^3	AST	242 IU/L
RBC	240×10^4 mm^3	ALT	129 IU/L
Hb	8.3 g/dL	TP	6.1 g/dL
Plt	12.5×10^4 mm^3	Alb	4.2 g/dL
Coagulation system		BUN	42.1 mg/dL
HPT	41.5%	Cr	2.09 mg/dL
APTT	15.6 s	T-Bil	30.0 mg/dL
PT	50.6%	D-Bil	24.8 mg/dL
INR	1.75	CRP	6.2 mg/dL
Blood gas analysis (O_2canula 2 L/min)		Na	130 mEq/dL
pH	7.369	K	5.0 mEq/dL
PaO_2	59.0 mm Hg	Others	
$PaCO_2$	30.7 mm Hg	IL-18	645.7 pg/mL
HCO_3^-	17.3 mmol/L	Cystatin C	4694.0 ng/dL
BE	–7.1 mmol/L		

Alb, albumin; APTT, activated partial thromboplastin time; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BE, base excess; BUN, blood urea nitrogen; Cr, creatinine; CRP, C-reactive protein; D-Bil, direct bilirubin; Hb, hemoglobin; HPT, hepaplastin test; IL, interleukin; INR, international normalized ratio; Plt, platelet; PT, prothrombin time; RBC, red blood cell; T-Bil, total bilirubin; TP, total protein; WBC, white blood cell.

postoperative day 61, and blood pressure also decreased to 87/55 mm Hg, infusion of dopamine (5 μg/kg/min) and furosemide + mannitol was started on postoperative day 62. Still having oliguria and hepatic coma on postoperative day 63, the patient was diagnosed with hepatorenal syndrome (Table 1). Thus, we decided to perform PDF in the intensive care unit (ICU) to remove both protein-bound substances and nephrotoxic substances simultaneously. An Evacure EC-2A plasma separator (Kuraray, Tokyo, Japan) was used, and the PDF session lasted 8 h. The blood flow rate was 100 mL/min. Filtered replacement fluid for artificial kidneys (Na^+, 140.0 mEq/L; K^+, 2.0 mEq/L Ca^{2+}, 3.5 mEq/L; Mg^{2+}, 1.0 mEq/L; Cl^-, 111.0 mEq/L; CH_3COO^-, 3.5 mEq/L; HCO_3^-, 35.0 mEq/L; $C_6H_{12}O_6$, 100 mg/dL) (Sublood-BS, Fuso Pharmaceutical, Osaka, Japan) was infused at a dialysate flow rate of 1000 mL/h and a replacement flow rate of 1000 mL/h. FFP (15 units) was also infused intravenously over 8 h. Nafamostat mesilate (Futhan, Torii Pharmaceutical, Tokyo, Japan) (30 mg/h) was used as an anticoagulant (Fig. 1) (6,8).

After one session of PDF, the patient's respiration and hemodynamics improved markedly. After two sessions of PDF, the patient was discharged from the ICU. After undergoing four sessions of PDF and three sessions of HDF, the patient recovered from hepatorenal syndrome (Fig. 2). A PAN membrane

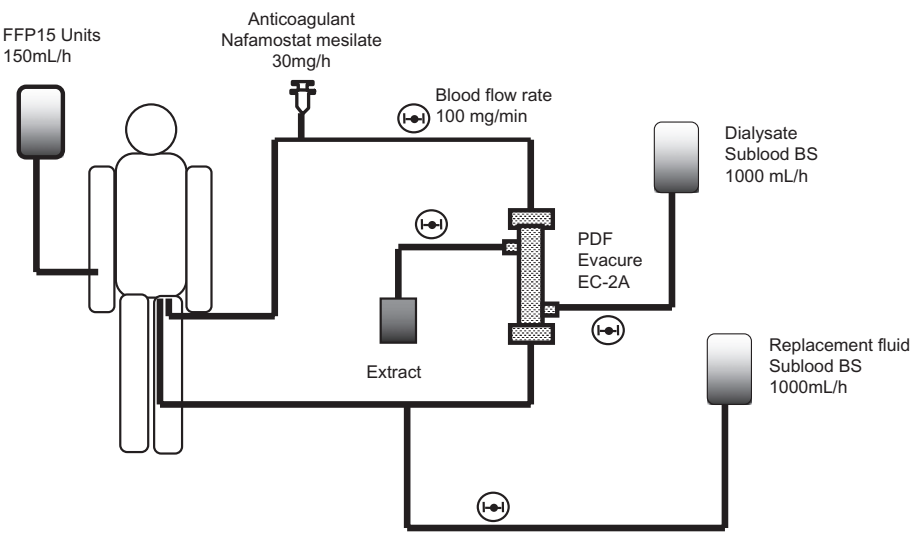

FIG. 1. Schematic representation of the flow of plasma diafiltration. FFP, fresh frozen plasma; PDF, plasma diafiltration.

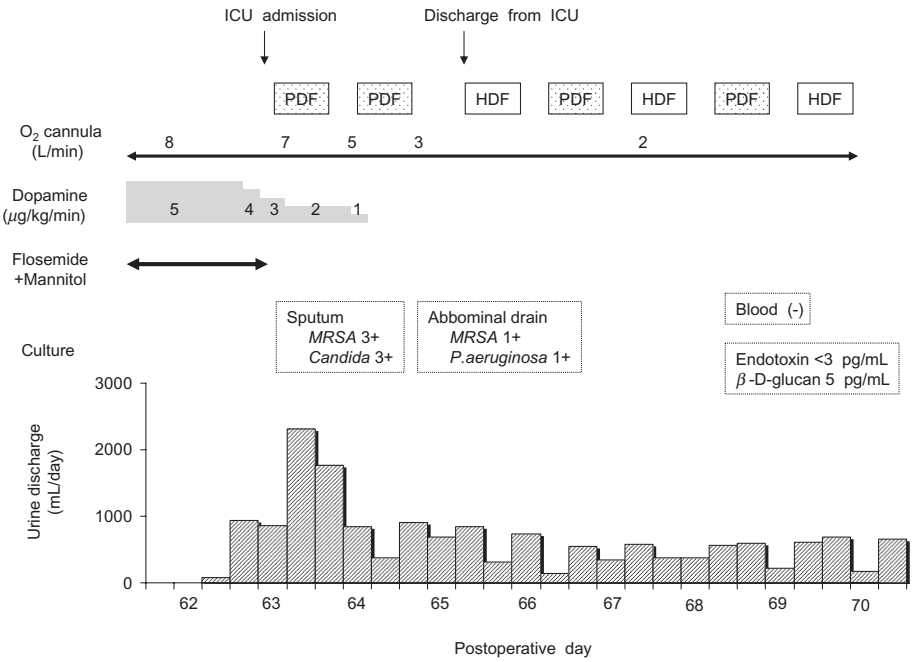

FIG. 2. Clinical course and treatment of the patient. Candida, *Candida albicans*; HDF, hemodiafiltration; MRSA, methicillin-resistant *Staphylococcus aureus*; P. aeruginosa, *Pseudomonas aeruginosa*; PDF, plasma diafiltration.

(Panflo APF-06S, Asahi Medical, Tokyo, Japan) was used as the hemofilter for HDF.

Laboratory values before and after PDF (mean of four measurements) were as follows. The total bilirubin level was reduced to 16.4 ± 2.5 mg/dL from 23.5 ± 3.7 mg/dL. The interleukin (IL)-18 level was reduced to 436.8 ± 25.5 pg/mL from 627.9 ± 39.5 pg/mL ($P = 0.0022$ and $P = 0.0047$, respectively). IL-18 levels were determined with an enzyme linked immunosorbent assay (ELISA; MBL, Nagoya, Japan), the detection limit of which is 12.5 pg/mL (normal, 126 ± 44.5 pg/mL). The citric acid concentration was increased to 7.4 ± 1.3 mg/dL from 4.0 ± 0.8 mg/dL ($P = 0.0020$, Fig. 3). The bilirubin removal rate was 29.9%, and the increase in the citric acid concentration was 46.4%. The blood urea nitrogen (BUN) level was significantly reduced to 21.0 ± 8.8 mg/dL from 29.2 ± 11.2 mg/dL, the creatinine level was significantly reduced to 1.3 ± 0.3 mg/dL from 1.6 ± 0.4 mg/dL, and the cystatin C level was significantly reduced to 2250.5 ± 465.8 ng/mL from 3493.3 ± 996.6 ng/mL ($P = 0.0088$, $P = 0.0146$, and $P = 0.0453$, respectively, Fig. 4). The cystatin C level was measured by ELISA (BioVendor, Brno, Czech Republic). Normal cystatin C levels are 1081.9 ± 304.7 ng/mL. There were no significant differences in the total protein and albumin levels before and after PDF ($P = 0.2312$ and $P = 0.8373$,

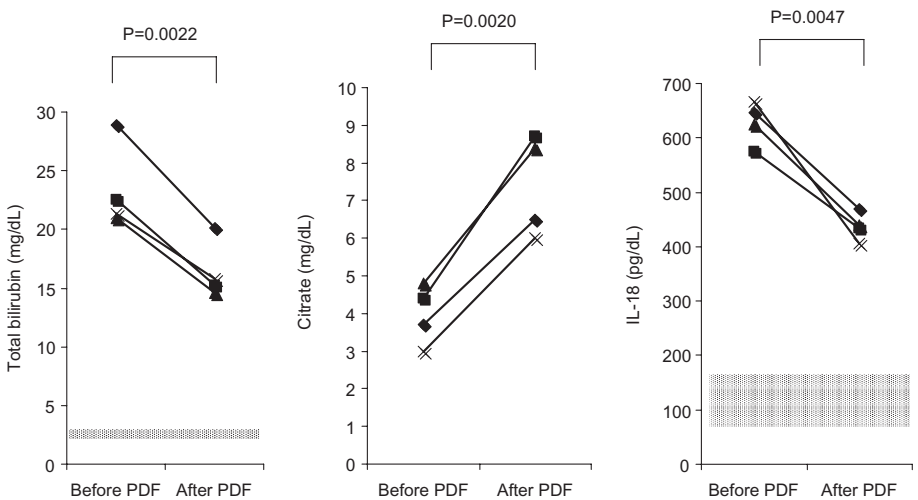

FIG. 3. Changes in total bilirubin, citrate, and interleukin (IL)-18. The cross hatched square shows the normal range. PDF, plasma diafiltration.

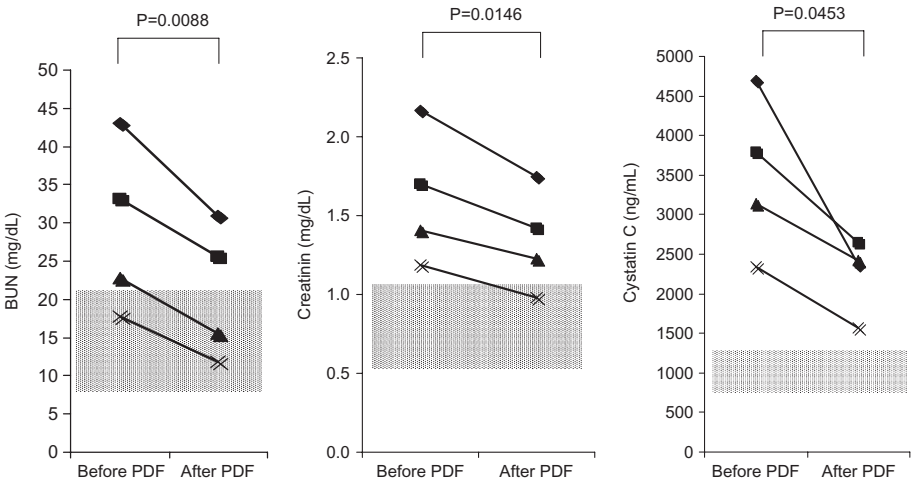

FIG. 4. Changes in blood urea nitrogen (BUN), creatinin, and cystatin C. A hatching square shows the normal range. PDF, plasma diafiltration.

respectively, Fig. 5). Values are expressed as mean ± SD. The significance of differences was assessed by the paired *t*-test, and *P*-values of <0.05 were considered statistically significant.

DISCUSSION

The Evacure EC-2A plasma separator used for PE in our patient has a pore size of 0.01 μm, which is much smaller than that of the standard plasma separation membrane (0.2–0.3 μm). This membrane has a sieving coefficient of 0.3 for albumin and thus can selectively remove low- or intermediate-molecular weight albumin-bound substances. In addition, coagulation factors are preserved because this membrane has a sieving coefficient of 0 for fibrinogen (9). In our patient, significant bilirubin was removed, and creatinine and cystatin C were also removed. In addition, it was found that IL-18 (10), which is involved in the pathology of hepatic failure, could also be removed. Cystatin C has drawn recent attention as a marker of early glomerular injury that is not affected by muscle mass, and so on (11,12). In our patient, the creatinine level was reduced to within the normal range, while the cystatin C level remained above the normal range. This may be because there is a creatinine-blind range, in which the blood concentration of creatinine (molecular weight, 0.1 kDa) does not increase until the glomerular filtration rate (GFR) reaches 31–50 mL/min, whereas the blood concentration of cystatin C (molecular weight: 13 kDa) increases when the GFR is 51–70 mL/min. In our patient, it might have been better to continue HDF until the cystatin C concentration, rather than the creatinine level, returned to normal.

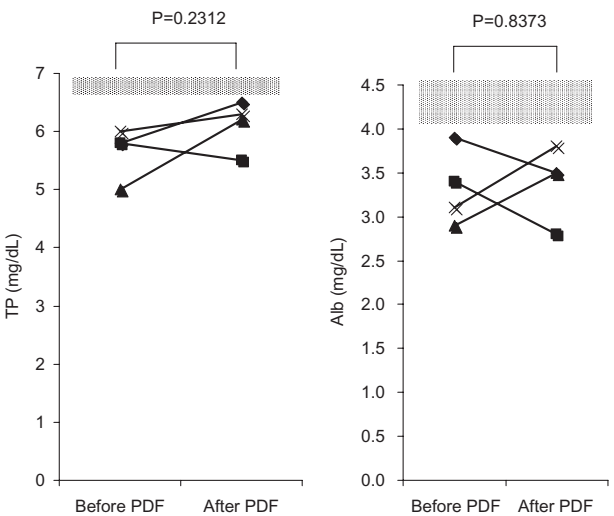

FIG. 5. Changes in total protein and albumin. The cross hatched square shows the normal range. Alb, albumin; PDF, plasma diafiltration; TP, total protein.

With PE, it is difficult to completely control an increase in the citric acid concentration even if CHDF is performed concomitantly with administration of large doses of FFP; whereas with PDF, the increase in the citric acid concentration was inhibited more effectively because smaller doses of FFP were required and because HDF was performed simultaneously. In addition, use of smaller doses of FFP led to lower medical costs (Table 2). The PDF conditions leave much room for improvement because the bilirubin removal rate with PDF is inferior to that with PE + CHDF.

In several countries, albumin dialysis using the molecular adsorbent recirculating system (MARS), fractionated plasma separation and adsorption (Prometheus system), and so on, are commonly

TABLE 2. *Comparison between PDF and PE + CHDF*

Method	PDF	PE + CHDF (Series parallel)
Plasma separator	Evacure EC-2A EVAL Film area 1.0 m^2, ϕ 0.01 μm	Plasmaflo PE (surface:EVAL) Film area 0.8 m^2, ϕ 0.3 μm
Hemofilter	(–)	Panflo APF-10S
FFP (/day)	15 units (1.2 L)	40–50 units (3.2–4.0 L)
Replacement fluid + dialysate (/day)	16L (16L/8 h)	16L (5.3 L/8 h)
Citrate increase (%)	46.4% ($N = 4$)	84.6% ($N = 55$)
Bilirubin removal (%)	29.9% ($N = 4$)	54.3% ($N = 56$)
Material cost (/procedure)	¥110 816 (US$965)	¥295 268 (US$2 570)

CHDF, continuous hemodiafiltration; FFP, fresh frozen plasma, PDF, plasma diafiltration; PE, plasma exchange.

performed in patients with hepatorenal syndrome for the purpose of removing hepatotoxic substances and nephrotoxic substances simultaneously (13–15). The MARS or Prometheus system, however, costs more and involves more complicated preparation than PDF. Overall, our case suggests that PDF may turn out to be the most useful blood purification therapy for hepatorenal syndrome in terms of medical economics. A study should be conducted in a larger number of cases for the therapy we report here to be established. At present, a multicenter study, in which we also participate, is underway.

REFERENCES

1. Nakae H, Yonekawa T, Narita K, Endo S. Are proinflammatory cytokine concentrations reduced by plasma exchange in patients with severe acute hepatic failure? *Res Commun Mol Pathol Pharmacol* 2001;109:65–72.
2. Nakae H, Yonekawa C, Wada H, Asanuma Y, Sato T, Tanaka H. Effectiveness of combining plasma exchange and continuous hemodiafiltration (combined modality therapy in a parallel circuit) in the treatment of patients with acute hepatic failure. *Ther Apher* 2001;5:471–5.
3. Nakae H, Asanuma Y, Tajimi K. Cytokine removal by plasma exchange with continuous hemodiafiltration in critically ill patients. *Ther Apher* 2002;6:419–24.
4. Nakae H, Yonekawa C, Moon S, Tajimi K. The series-parallel circuit in the treatment of fulminant hepatitis. *Ther Apher Dial* 2004;8:153–9.
5. Yonekawa C, Nakae H, Tajimi K, Asanuma Y. Effectiveness of combining plasma exchange and continuous hemodiafiltration in patients with postoperative liver failure. *Artif Organs* 2005; 29:324–8.
6. Nakae H, Igarashi T, Tajimi K. The dose of nafamostat mesilate during plasma exchange with continuous hemodiafiltration in the series-parallel circuit. *Ther Apher Dial* 2006;10: 233–6.
7. Mori T, Eguchi Y, Shimizu T et al. A case of acute hepatic insufficiency treated with novel plasmapheresis plasma diafiltration for bridge use until liver transplantation. *Ther Apher* 2002;6:463–6.
8. Nakae H, Tajimi K. Pharmacokinetics of nafamostat mesilate during continuous hemodiafiltration with a polyacrylonitrile membrane. *Ther Apher Dial* 2003;7:483–5.
9. Kuraray Medical. *Evacure Plasmapheresis System*. [Cited 29 Jul 2006.] Available from URL: http://www.kuraray.co.jp/Medical
10. Nakae H, Zheng Y-J, Wada H, Tajimi K, Endo S. Involvement of IL-18 and soluble fas in patients with postoperative hepatic failure. *Eur Surg Res* 2003;35:61–6.
11. Newman DJ. Cystatin C. *Ann Clin Biochem* 2002;39:89–104.
12. Shimizu-Tokiwa A, Kobata M, Io H et al. Serum cystatin C is a more sensitive marker of glomerular function than serum creatinine. *Nephron* 2002;92:224–6.
13. Kurtovic J, Boyle M, Bihari D, Riordan SM. An Australian experience with the molecular adsorbents recirculating system (Mars). *Ther Apher Dial* 2006;10:2–6.
14. Evenepoel P, Laleman W, Wilmer A et al. Prometheus versus molecular adsorbents recirculating system: comparison of efficiency in two different liver detoxification devices. *Artif Organs* 2006;30:276–84.
15. Rifai K, Manns MP. Review article: clinical experience with Prometheus. *Ther Apher Dial* 2006;10:132–7.