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Effect of Therapeutic Plasmapheresis by Plasma Exchange and Plasma Adsorption in Postoperative Liver Failure Following Abdominal Surgery

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Introduction

Plasmapheresis has been used as the most effective and the final therapeutic choice for postoperative liver failure patients after abdominal surgery, especially in cases of hepatobiliary disease.[1,2] However, postoperative liver failure easily develops into multiple organ failures (MOF), and the success rate of plasmapheresis is not sufficient as a routine therapeutic modality. In this study, a recent result of plasmapheresis was evaluated retrospectively in order to know "When to start plasmapheresis?," "Which patient is responsive to plasmapheresis?," and "How to select the patient?," Plasma delta bilirubin level was evaluated as a marker of postoperative hyperbilirubinemia and a monitor for plasmapheresis.[3,4]

Also a specific removal method is required to be developed in place of plasma exchange in order to avoid various infectious diseases transmitted by fresh-frozen plasma (FFP) and to decrease the medical cost of FFP. The result of bilirubin removal by a newly developed plasma adsorption (PA) column for bilirubin removal, containing a porous type anion exchange resin coated with hydroxyethylmetacrylate (HEMA) copolymer,[5,6] were compared with bilirubin removal by the plasma exchange (PE).

Methods

Patients. From January 1981 to March 1992, we managed 35 patients with postoperative liver failure by plasmapheresis. Severe liver dysfunction was defined by the same criteria as hepatic encephalopathy >grade 2 and/or a decreased activated clotting time <40% and/or an increased serum bilirubin level >10 mg/dl (5 mg/dl in cases of hepatectomy in recent cases), and conditions resistant to the conventional drug therapy.

Plasmapheresis procedure. The basic treatment schedule was three times per week. Therapeutic plasmapheresis was performed mainly by PE using a membrane separator and FFP as a substitutional fluid. Exchange blood transfusion and direct hemoperfusion using charcoal column were used at first in four patients, but showed poor effect and were changed to PE. In two recent hyperbilirubinemia patients, both PA using the resin column (Medisorba BL-300, Kurare) and the PE was performed alternately in a series of plasmapheresis. One calculated and one and a half calculated plasma volume were processed in PE and PA respectively. Heparin was used as a systemic anticoagulant, and nafamostat mesilate was used when a patient showed hemorrhagic diathesis. Plasmapheresis was repeated until the improvements in the basic protocol were attained.

Evaluation of plasmapheresis. Response to plasmapheresis was divided into three groups by the result of survival: "recovered" indicates recovered cases who were discharged from the hospital after complete recovery from postoperative liver failure, "responsive" indicates patients who survived over 1 month after starting plasmapheresis, and "poor" indicates non-Effective cases other than these two categories. "effective" includes both recovered and responsive. The time point and serum bilirubin level at the point of initiating plasmapheresis, total times of plasmapheresis procedures, and the variety of disease condition were analyzed in these three groups.

Plasma samples were taken before and after the PE and PA procedure on the same patients, and for the analysis of bilirubin removal, delta bilirubin (Bd), monoconjugated B (MCB), diconjugated B (DCB), and unconjugated B (BU) were measured using HPLC.[7] Micronex RP30 column (Sekisuikagaku, Osaka, Japan) was used at 450 nm (optical density, OD). The ratio of Bd to the sum of conjugated bilirubin (Bd/(Bd+MCB+DCB)) was calculated.

Table 1 Effect of plasmapheresis and background disease and conditions to develop postoperative liver failure (number of patients).

Evaluation	Hepatectomy		Pancreatobiliary ope.		Esophageal varices	
	I/MOF	LC	I/MOF	LC	I/MOF	LC
Effective	0*	6	6	4	0*	1
Poor	3	2	4	1	3	0

I, infection: MOF, multiple organ failures: I/MOF, I and/or MOF: LC, liver cirrhosis: ope., operation.
*$P<0.05$, chi-square analysis.

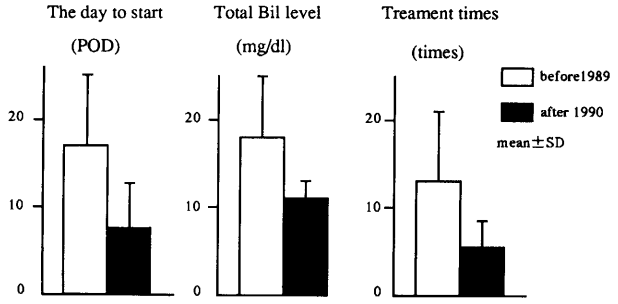

Fig. 1 Conditions to initiate plasmapheresis in recovered cases. Mean±SD, n.s.

Statistical significance was calculated with Student's *t*-test and chi-square test.

Results

Of the 35 patients, 10 (28.5%) recovered after 2 to 38 treatments, 10 cases (28.5%) were responsive after 3 to 125 treatments, and 20 cases (57%) were effective. Fifteen cases (43%) showed poor results after 2 to 10 treatments. The day and the serum level of total bilirubin at starting plasmapheresis and times of plasmapheresis treatment did not show any statistically significant differences among the three groups.

The results related to the underlying disease were as follows: 6/25 cases with malignant disease and 4/10 cases with benign disease were recovered, and no difference was observed in efficacy. The operation was divided into 5 categories. In these categories, 7/12 cases of hepatectomy, 7/12 cases of pancreatobiliary operation, 1/4 cases of esophageal varices, and 2/3 cases of MOF were judged to be effective. The operation themselves did not affect the success rate of plasmapheresis. The complications which caused postoperative liver failure were divided into 7 categories. In these categories, 10/18 cases of infection, 9/18 cases of liver cirrhosis, 2/11 cases of MOF, 2/12 cases of overlapping of these three categories, 2/2 cases of over-size resection in hepatectomy, and 0/1 case of reoperation were judged to be effective. The MOF group showed a lower success rate than the infection group ($P<0.05$). The result of the combination of the category of operation and the complication was shown in Table 1. The combination of infection and/or MOF in both the hepatectomy and the esophageal varices groups showed a poor response ($P<0.05$). Conversely, the combination of infection and/or MOF in the pancreatobiliary operation group was not an independent risk factor.

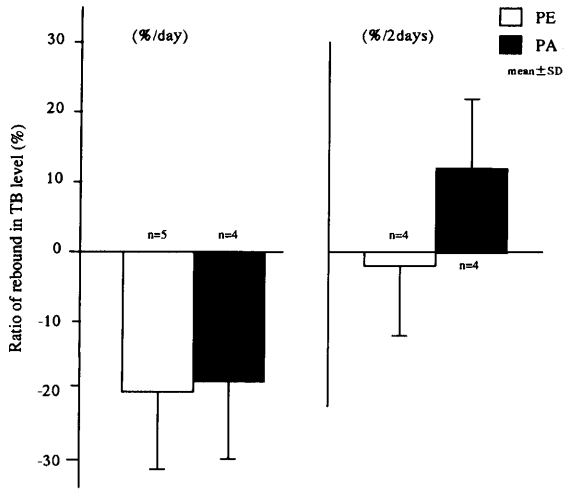

Fig. 2 Percent changes of rebound in plasma total bilirubin level after PE and PA in two cases. Mean±SD, n.s.

A strict protocol to start the plasmapheresis treatment at an earlier point of postoperative liver failure has been started from 1990. So far 10 patients have been treated since 1990. Six out of 10 patients (60%) were recovered and 1/10 patients was responsive, showing higher effectiveness of plasmapheresis than 4/25 (16%) before 1989 with statistical significance ($P<0.05$). The condition to start plasmapheresis and the times of treatment in recovered cases after 1990 were lower than the former recovered cases (Fig. 1).

The result of *in vivo* PA showed the same selectivity in the decrease in the serum bilirubin level as PE in the same patients. Post/pre changes in PA showed more reduction in conjugated bilirubin: 21.4±16.7% of MCB, 30.8±8.6% of DCB, respectively. In contrast, there was a smaller reduction in Bd and BU, 85.7±14.1% and 73.7±31.9% respectively, than that of total

bilirubin (52.2±7.6%, $P<0.05$). As a result, the ratio of Bd/(Bd+MCB+DCB) after PA increased to 178.6±36.8% compared with 123.3±43.7% after PE ($P<0.05$). There was no difference in the percent ratio of bilirubin reduction in patient's plasma between PE (52.2±7.9%) and PA; however, the rebound after PA was higher than after PE in case 2 (Fig. 2). The patients complained of fatigability more often after PA than after PE without changes in vital signs or serum electrolyte levels. No difference of blood count was observed during the plasmapheresis (data not shown).

Discussion

Our results of plasmapheresis showed 57% effectiveness in all patients. However, the complication of severe infection and/or MOF in patients with liver cirrhosis shows poor response. Also, to start plasmapheresis at an earlier stage is important for the complete recovery. In a recent protocol, we decreased treatment times and it is effective to decrease medical costs and possibly the risk of infection from FFP.

Delta bilirubin measurement is an effective marker for the evaluation of the plasmapheresis.[1,2] It has been shown that Bd is a potent monitoring parameter before and during plasmapheresis.[3,4] Also, Bd suggested that the effective case had a different quality of hyperbilirubinemia and a different condition of the disease before plasmapheresis and also a different response to plasmapheresis.

The result of *in vitro* PA by the resin showed the selectivity of bilirubin removal compared to the other molecules measured.[5] *In vivo* analysis revealed the difference of removal in bilirubin fractions and that of bilirubin rebound. The resin is effective for the selective bilirubin removal in PA and it causes metabolic effects of bilirubin fractions, however more detailed and long-term evaluation of the effectiveness of PA therapy is required.

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