Clinical Reports on Plasma Exchange in the Kidney Center, Tokai University School of Medicine

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There were 72 patients (19 with hepatic failure, 10 with fulminant hepatitis, eight with paraquat poisoning, eight with rheumatoid arthritis, five with myasthenia gravis, four with hyperlipidemia, four with systemic arteriosclerosis including brain infarction, three with pemphigus vulgaris, two with multiple myeloma, two with systemic lupus erythematosus, two cases non-specific Ig-G antibody, two cases medication with an anticancer drug, one with multiple sclerosis, one with Crohn's disease with amyloid kidney and one with chronic myeloblastic leukemia) treated by plasma exchange in the Kidney Center, Tokai University School of Medicine from Jan. 1983 to Dec. 1986.

We performed plasma exchange using fresh frozen plasma in 40 cases and Lactate-Ringer's solution containing albumin (4.0—5.0%) in 20 cases as the replacement fluid. In 17 cases, we performed double filtration plasma exchange with the recycle system and no replacement fluid.

Although PE therapy did not constitute a basic therapy for hyperlipidemia, pemphigus vulgaris, rheumatoid arthritis, myasthenia gravis, and systemic lupus erythematosus, it was effective in relieving severe clinical symptoms.

At the present time, conventional plasma exchange does not improve the survival rate of patients with hepatic failure and fulminant hepatitis. Developments of a new artificial liver support apparatus and identity of many toxic substances in hepatic failure are necessary.

No hypotension, hypovolemic shock or other significant complications were experienced.

(Key Words: Plasma exchange therapy, replacement fluid, double filtration plasmapheresis)

INTRODUCTION
Since plasmapheresis was described in 1914 by Abel and colleagues at Johns Hopkins University (1), therapeutic plasmapheresis has played a major role in the treatment of intractable diseases and the investigation of their causes. Following the development of new high performance membranes for hemodialysis and/or hemofiltration, membrane plasma separation devices began to appear in the 1970s (17). The simplicity and safety of membrane plasma separation in plasmapheresis has led to its recent widespread acceptance and because of their close similarity to hemodialysis, membrane separators have become widely used in kidney centers for plasmapheresis.

This paper reports on our performances of plasma exchange (PE) and double filtration PE (DFPE) in 72 patients with various diseases using membrane filters.

PATIENTS AND METHODS
Patients: PE and DFPE cases in the Kidney Center, Tokai University School of Medicine were collected in the four year period from 1983 through 1986. Effects of PE therapy were studied in 72 cases including 19 with hepatic failure, 10 with fulminant hepatitis, eight with paraquat poisoning, eight with rheumatoid arthritis (RA), five with myasthenia gravis (MG), four with hyperlipidemia, four with systemic arteriosclerosis with brain infarction, three with pemphigus vulgaris (PV), two with multiple myeloma (MM), two with systemic lupus erythematosus (SLE), two cases with non-
specific Ig-G antibody, two with malignant tumors, one with multiple sclerosis, one with Crohn's disease with amyloid kidney and one with chronic myeloblastic leukemia (Table 1).

**Plasma Exchange:** The patients' blood was drawn and separated into corpuscles and plasma via the first separation filter (PE). The separated plasma was then passed through the second filter (DFPE). The filtered plasma and separated blood cells were circulated back into the patients.

Poly-vinyl alcohol (PVA; Plasmacure, Kurary), cellulose-diacetate (Plasmaflow, Asahi) and poly methyl methacrylate (PMMA; Plasmax PS-05, Toray) membrane filters were used as the first filter membrane, and an ethylene-vinyl alcohol (EVAL, Evaflux, Kurary), cellulose-diacetate (Cascadeflo, Asahi) and PMMA (Plasmax QS, Toray) membrane filters as the second one.

Each PE or DFPE treatment lasted 3 hours and the plasma separation volume was about 3,000 ml.

PE was performed using fresh-frozen plasma (FFP) and DFPE with 4.0 – 5.0% albumin in Lactac solution in 20 cases and no replacement fluid in 17 cases (Table 2).

### Table 1 Patients treated by plasmapheresis

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hepatic failure</td>
<td>19 (26.4)</td>
</tr>
<tr>
<td>2 Fulminant hepatitis</td>
<td>10 (13.9)</td>
</tr>
<tr>
<td>3 Paraquat poisoning</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>4 Rheumatoid arthritis</td>
<td>8 (11.1)</td>
</tr>
<tr>
<td>5 Myasthenia gravis</td>
<td>5 (6.9)</td>
</tr>
<tr>
<td>6 Hyperlipidemia</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>7 Systemic arteriosclerosis</td>
<td>4 (5.6)</td>
</tr>
<tr>
<td>8 Pemphigus vulgaris</td>
<td>3 (4.2)</td>
</tr>
<tr>
<td>9 Multiple myeloma</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>10 Systemic lupus erythematosus</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>11 Non-specific Ig-G antibody</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>12 Anticancer chemotherapy*</td>
<td>2 (2.8)</td>
</tr>
<tr>
<td>13 Multiple sclerosis</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>14 Crohn's disease</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>15 Chronic myeloblastic leukemia**</td>
<td>1 (1.4)</td>
</tr>
<tr>
<td>Total</td>
<td>72 (100.0)</td>
</tr>
</tbody>
</table>

*Removal of CDDP
(Kidney Center, Tokai University 1983–1986)

**ABO blood-group incompatibility between donor and recipient by bone marrow transplantation

### Table 2 Replacement fluids

<table>
<thead>
<tr>
<th>Replacement fluids</th>
<th>No. of cases*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fresh frozen plasma (FFP)</td>
<td>40</td>
</tr>
<tr>
<td>Lactate-Ringer's solution</td>
<td>20</td>
</tr>
<tr>
<td>containing albumin (4.0–5.0%)</td>
<td></td>
</tr>
<tr>
<td>Replacement fluid free</td>
<td>17</td>
</tr>
</tbody>
</table>

*including double cases
RESULTS

(1) Hepatic failure
Among the 19 hepatic failure cases, 17 (89.5%) were males aged 20—78 years (average age: 55.6 years) and two (10.5%) females aged 52 and 64 years (male to female ratio was 8.5 : 1). Causes of hepatic failure were nine malignant tumors (four hepatomas, two pancreas head carcinomas, two gallbladder carcinomas and one lung cancer), five postoperative multiorgan failures, three liver cirrhosis and subacute hepatitis.

PE lasted about 3 hours, and 3 to 4 liters of FFP were used as the replacement fluid. Blood flow was 100 ml/min, and the flow of separated plasma was about 30 ml/min. We performed PE and direct hemoperfusion (DHP) therapy in two patients. If consciousness was not recovered during the 1st week of treatment, the prognosis was usually very bad.

Seventeen patients treated by PE died, only two patients recovered and the survival rate was 10.5% (Table 3).

Direct causes of death were seven bleeding tendencies (gastrointestinal (GI) bleeding, DIC), three hepatic failures, three infections (sepsis, pneumonia), one pulmonary edema and one uremia.

(2) Fulminant hepatitis
Among the 10 fulminant hepatitis cases, six (60%) were males aged 20—83 years (average: 54.5 years) and four (40.4%) females aged 20-67 years (average: 42.5 years) (male to female ratio 1.5 : 1). Seven patients died, three patients recovered, and the survival rate was 30.0% (Table 3).

We scheduled PE and PE with DHP therapy for hepatic failure patients.

Direct causes of death were three bleeding tendencies (DIC, GI bleeding), two brain damages and two hepatic failures.

(3) Paraquat poisoning
Among the eight paraquat poisoning cases, four (50.0%) were males aged 32—49 years (average: 43.5 years) and four (50.0%) females aged 27—62 years (average: 39.8 years) (male to female ratio 1 : 1). Six patients die, two patients recovered, and the survival rate was 25.0%. Direct cause of death was acute respiratory failure.

We performed PE (3 to 4 liters of FFP were used) and DHP therapy in all patients and continuous slow hemofiltration (CSHF) in two patients with MOF including acute renal failure (ARF).

(4) Rheumatoid arthritis (RA)
Among the eight RA cases, three (37.4%) were males aged 48, 64 and 69 years and five (62.6%) females aged 45—57 years (average age: 52.2 years) (male to female ratio 1 : 1.7).

Table 3 Efficacy in plasmapheresis therapy

<table>
<thead>
<tr>
<th>Diseases</th>
<th>No. of cases (Efficacy rate %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Hyperlipidemia</td>
<td>4 (100.0)</td>
</tr>
<tr>
<td>2 Pemphigus vulgaris</td>
<td>3 (100.0)</td>
</tr>
<tr>
<td>3 Non-specific Ig-G antibody</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>4 Anticancer chemotherapy</td>
<td>2 (100.0)</td>
</tr>
<tr>
<td>5 Crohn's disease</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>6 Chronic myeloblastic leukemia</td>
<td>1 (100.0)</td>
</tr>
<tr>
<td>7 Rheumatoid arthritis</td>
<td>7 (87.5)</td>
</tr>
<tr>
<td>8 Myasthenia gravis</td>
<td>3 (60.0)</td>
</tr>
<tr>
<td>9 Systemic arteriosclerosis</td>
<td>2 (50.0)</td>
</tr>
<tr>
<td>10 Multiple myeloma</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>11 SLE</td>
<td>1 (50.0)</td>
</tr>
<tr>
<td>12 Fulminant hepatitis</td>
<td>3 (30.0)</td>
</tr>
<tr>
<td>13 Paraquat poisoning</td>
<td>2 (25.0)</td>
</tr>
<tr>
<td>14 Hepatic failure</td>
<td>2 (10.5)</td>
</tr>
<tr>
<td>15 Multiple sclerosis</td>
<td>doubtful</td>
</tr>
</tbody>
</table>
All patients received three DFPEs for 3 days and a single DFPE at monthly intervals. We used Kuraray's KM-8500 system with the EVAL "4A" or "3A" membrane as the second filter. No substitute fluid was administered to the patients because we performed DFPE with the recyle system (8).

Clinical symptoms (morning stiffness, arthralgia in various joints) were markedly improved by DFPE and the effects remained for a long time except for one 48 year-old male patient.

(5) Myasthenia gravis (MG)

We treated five MG patients (two males, and three females), aged 29 - 65 years (average age: 44.8 years).

We performed DFPE with the EVAL "2A" membrane as the second filter. All patients received three DFPEs twice for 3 days during 2 weeks.

We used 4 - 5% albumin in Lactac solution as the replacement fluid. Clinical symptoms (arm elevation time, grip strength) were improved by DFPE in three (60.0%) of our patients (9).

(6) Hyperlipidemia

DFPE therapy was performed on four hyperlipidemia patients (three with familial hypercholesterolemia and one uremic patient with hypertriglyceridemia) including two males aged 39 and 52 years and two females aged 55 and 62 years.

We used EVAL "4A" membrane as the second filter and no substitute fluid was administered to the patients. One patient received one DFPE and one DFPE with selective LDL absorption (8).

In the cases of familial hypercholesterolemia, the removal rates of total cholesterol and HDL-cholesterol were 40 - 50% and 10 - 20%, respectively.

We think DFPE is effective in treatment by reducing of the risk of coronary heart disease of hyperlipidemia.

(7) Systemic artherosclerosis with brain infarction

DFPE therapy was performed on two male systemic arteriosclerosis cases with brain infarction aged 57 and 68 years and two male systemic arteriosclerosis patients aged 50 and 51 years. All patients received three DFPEs for 3 days and clinical symptoms including gait disturbance, speech disturbance and grip were improved by DFPE.

(8) Pemphigus vulgaris (PV)

Three PV patients were selected for DFPE therapy. We used EVAL "2A" membrane as the second filter. Lactate-Ringer's solution containing albumin (4.0%) replaced the drained plasma. All three patients' clinical symptoms improved in conjunction with a decrease in the antipidermal cell membrane antibody titer (5).

(9) Multiple myeloma (MM)

DFPE therapy was performed on two male MM patients aged 55 and 64 years with renal insufficiency, hyperviscosity syndrome and disturbance of consciousness. We used EVAL "4A" and "2A" membrane as the second filter.

One of the two patients recovered from disturbance of consciousness, but the patients died due to acute pancreatitis and G-I bleeding.

(10) Systemic lupus erythematosus (SLE)

DFPE therapy was performed on two female SLE patients aged nine and 42 years.

A 9 year-old female was admitted to our hospital in a coma. After admission, she was treated by DFPE at five sessions in two weeks. The coma markedly improved, but she succumbed to respiratory failure 2 months after admission. A 42 year-old female with renal failure was started on regular hemodialysis with DFPE at three sessions a week and one per week for 4 weeks. Clinical symptoms were not changed by DFPE and she died due to GI bleeding and hyperkalemia.

(11) Non-specific Ig-G antibody

DFPE therapy was performed on two patients with non-specific Ig-G antibody.

A 67 year-old woman with right renal cell carcinoma could not be transfused with blood because of non-specific IgG antibody and direct Coombs' positivity. After three sessions of DFPE, nephrectomy was carried out. Since blood loss was massive, washed RBCs were transfused. The post operative course was uneventful and Coombs' test was negative after surgery (14). A 33 year-old woman with malignant...
melanoma of the uterus could not be transfused with blood because of non-specific IgG antibody and direct Coombs' positivity. Washed RBCs were transfused due to severe anemia after three sessions of DFPE. The post-transfusion course was uneventful.

(12) Anticancer chemotherapy
PE therapy were performed on two patients due to withdrawal of the anticancer drug, cis-diaminedichloplatinum (CDDP) (11).
A 53 year-old man with peritonitis carcinomatosa due to gastric cancer under maintenance hemodialysis (HD) was treated by CDDP. Since he was an HD patient, we performed PE using 4 liters of FFP because of removal of CDDP. PE was effective after withdrawal of CDDP and no significant side effects of CDDP and PE therapy were experienced.
A 43 year-old woman with ovarian cancer under HD was treated by CDDP after a radical operation. We performed PE using 4 liters of FFP and PE was effective after withdrawal of CDDP without significant side effects of CDDP and PE.

(13) Multiple sclerosis (MS)
Three sessions of DFPE using Latate-Ringer's solution containing albumin (5.0%) were performed on a 55 year-old woman diagnosed as MS. No significant effects of DFPE were experienced and she died due to GI bleeding.

(14) Crohn's disease with amyloidosis
A 22 year-old man diagnosed as Crohn's disease with amyloidosis was treated by DFPE. Since DFPE induction, his renal functions progressively deteriorated, but after DFPE three times per week, deterioration of his renal functions was stopped. His renal functions are stable one year after the initiation of DFPE. We performed DFPE using an EVAL 3A membrane as the second filter in one session per month for one year. We believe that DFPE is effective in the treatment of amyloid kidney.

(15) Chronic myeloblastic leukemia (CML)
A 14 year-old man was referred for treatment of CML by bone marrow transplantation and we performed immunoabsorption (Bio-Synsorb A) for removal of A and B blood-group antibodies because of ABO and blood-group incompatibility between donor (A, RH(+) and recipient (O, RH(+)). The patient subsequently had allogenic marrow infused without incident (10).

DISCUSSION
In the early 1960s, developments of continuous flow centrifugation techniques and in the 1970s, developments of membrane plasma separator devices occurred. Recently, DFPE, cryofiltration and specific immuno-absorbsents (plasmaperfusion) have been performed for increasing the selectivity of removal of pathological substances.
PE has been widely employed in several autoimmune diseases for the purpose of removing autoantibodies and immune complexes, and in hepatic failure for the purpose of removing hepatic toxic substances.
Although PE therapy is useful in reversing the coma of acute hepatic failure and fulminant hepatitis, statistic improvement of the long-term survival rate is unknown (7,12,13). In our data the survival rate was also very low despite improvement in the coma grade.
DFPE and/or cryofiltration were performed on RA patients who did not respond to conventional drug therapy and symptomatic improvements were demonstrated (4,15,21). In our data, improvements in arthralgia, swelling and stiffness of the joints were also demonstrated in all RA patients treated by DFPE.
The patient's symptoms improved with a decrease in autoantibody titer including anti-acetyl CoA antibodies in MG (9,16) and antiderminal cell membrane antibodies in PV (5,18,20). We also observed symptomatic improvements in patients with MG (60.0%) and PV (100.0%).
DFPE in the treatment of familial hypercholesteremia is effective in reducing the level of total-cholesterol with a low decrease rate of HDL-cholesterol in the blood, and DFPE is effective therapy for reduction of the level of triglyceride in the blood of patients with chronic renal failure maintained on hemodialysis (6,8,19).
We also reported that DFPE has been found effective in the treatment of Crohn's disease and cerebrovascular diseases and although the exact pathogenesis of MS is unknown, recent reports suggest that DFPE therapy is useful in...
treatment of MS (2,3).

We tried PE and/or DFPE for the treatment of many intractable diseases in 72 patients. In clinical applications of plasmapheresis, it is very important and necessary to clarify the pathogenesis of each disease, and determine indicators and optimal regimens for plasmapheresis.

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REFERENCES