Received: 25 March 2022 | Accepted: 22 June 2022

DOI: 10.1111/1744-9987.13906

ORIGINAL ARTICLE

Therapeutic Apheresis and Dialysis

WILEY

Real-world application of plasmapheresis for neurological disease: Results from the Japan-Plasmapheresis Outcome and Practice Patterns Study

Youwei Lin[1,2] | Satoru Oji[3] | Katsuichi Miyamoto[4] | Tomoko Narita[5] | Mana Kameyama[6] | Hidenori Matsuo[5,7]

[1]Department of Neurology, National Center Hospital, National Center of Neurology and Psychiatry, Kodaira, Japan

[2]Department of Immunology, National Institute of Neuroscience, National Center of Neurology and Psychiatry, Kodaira, Japan

[3]Department of Neurology, Saitama Medical Center, Kawagoe, Japan

[4]Department of Neurology, Kindai University Hospital, Osakasayama, Japan

[5]Department of Neurology, Nagasaki Kawatana Medical Center, Kawatana, Japan

[6]Clinical Development Department, Asahi-Kasei Medical Co., Tokyo, Japan

[7]Department of Neurology, Nagasaki National Hospital, Nagasaki, Japan

Correspondence
Youwei Lin, 4-1-1 Ogawahigashi, Kodaira, Tokyo 187-8502, Japan.
Email: lin@ncnp.go.jp

Abstract

Introduction: Plasmapheresis is a well-recognized treatment for autoimmune neurological diseases in Japan. However, the practice varies depending on the facility, and the actual treatment conditions are unclear.

Methods: To clarify real-world conditions, a prospective observational study was conducted on patients with neurological diseases who were scheduled to receive plasmapheresis. A dataset was analyzed that included 887 treatments from 210 patients with myasthenia gravis (MG), multiple sclerosis (MS), neuromyelitis optica spectrum disorders (NMOSD), and other diseases for 82, 30, 24, and 74 patients, respectively.

Results: The types of plasmapheresis performed included immunoadsorption plasmapheresis, plasma exchange, and double filtration plasmapheresis with 620, 213, and 54 treatments, respectively. Approximately, 60% of the treatments were performed using peripheral blood access alone. Non-serious adverse events were observed in 10 patients.

Conclusions: A statistically significant improvement was observed after plasmapheresis in patients with MG, MS, and NMOSD. These were evaluated using the modified Rankin Scale.

KEYWORDS

autoimmune neurological diseases, double filtration, immunoadsorption, plasma exchange, plasmapheresis

1 | INTRODUCTION

Recently, it has become clear that many neurological disorders are associated with immune abnormalities. Certain of these diseases are categorized as autoimmune diseases. Therefore, immune-related disease-modifying therapies, such as specific molecular targeted agents, have been developed. This has resulted in an improved prognosis for patients and has widened their therapeutic options [1–4]. A few options are available to control acute exacerbations of autoimmune diseases. Plasmapheresis is one of these. It is an extracorporeal circulation therapy to remove pathogenic molecules from the blood of patients with autoimmune disorders [5–8].

Plasmapheresis, including plasma exchange (PE), immunoadsorption plasmapheresis (IAPP), and double filtration plasmapheresis (DFPP), has been covered under Japanese public insurance since 1984. Insurance includes plasmapheresis coverage for myasthenia gravis (MG), multiple sclerosis (MS), Guillain–Barré syndrome (GBS), and chronic inflammatory demyelinating polyneuropathy (CIDP). Furthermore, the guidelines of the American Society for Apheresis [9] describe PE and IAPP as first- or second-line treatment options for many autoimmune neurological diseases. These can be used alone or in combination with other treatment options such as intravenous immunoglobulins and corticosteroids.

PE replaces the separated plasma from the patient's blood with a comparable amount of fresh frozen plasma (FFP) or albumin solution. DFPP removes large molecules from separated plasma by molecular size fractionation using a plasma separator. IAPP mainly removes immunoglobulin G (IgG) by separating the plasma. PE can remove substances in the patient's plasma non-specifically with a wide range of molecular weights while requiring a comparable volume of FFP or an albumin solution as the replacement fluid. DFPP separates and removes pathogenic substances while retaining valuable substances. Therefore, it requires a smaller volume of blood products than PE, such as albumin solution. IAPP does not require the administration of blood products. However, it does require the select removal of pathogenic substances that can be adsorbed onto the immunoadsorption column.

Despite their relatively high usage in clinical settings (especially in Japan), few prospective clinical studies have been performed on the application of plasmapheresis in patients with various autoimmune neurological diseases. In addition, treatment conditions vary depending on the facility and the clinician's experience. There are no standards or consensus for the specific application of plasmapheresis treatments regarding autoimmune neurological diseases. Therefore, we conducted this study to investigate the current status, safety guidelines, and clinical outcomes of plasmapheresis treatment for autoimmune neurological diseases. We analyzed these factors in a real-world setting in Japan to obtain the most beneficial information for the optimal management of plasmapheresis.

2 | PATIENTS AND METHODS

2.1 | Study design

The Japan-Plasmapheresis Outcome and Practice Patterns Study (J-POPPS) was a prospective and observational multi-center study conducted at 13 representative hospitals in Japan. Patients diagnosed with neurological diseases by multiple neurologists who underwent plasmapheresis were enrolled in the study. The inclusion criteria were as follows: (1) prescribed plasmapheresis by a neurologist; (2) aged 16 years or older; and (3) provision of written informed consent. Re-enrollment was authorized if the disease relapsed and the patient fulfilled the inclusion criteria. Treatments other than plasmapheresis, including medication, were not restricted during the study period. The case report form requested patient information, including demographics, medical history, specifics of the treatment, and the clinical outcome of plasmapheresis.

2.2 | Rate of receiving plasmapheresis and rate of inclusion

At first, all patients who received plasmapheresis in the 13 participating hospitals were planned to be enrolled in this study. However, it became clear that certain hospitals only partially enrolled potentially eligible patients due to the unavailability of timely patient consent or human resource shortages. Therefore, an additional survey was conducted to determine the inclusion rates of each hospital. Consequently, 12 of the 13 hospitals responded to the additional survey. The maximum enrollment was set at 50 due to the possibility of large inter-hospital variations in enrollment.

2.3 | Clinical outcome assessment

The modified Rankin Scale (mRS) [10] and Barthel Index (BI) [11] evaluations were applied to every patient twice: before and 15 to 31 days after completion of plasmapheresis. The mRS and BI were used to measure and compare clinical outcomes as a universal scale, in addition to a disease-specific scale for most of the diagnoses (i.e., MG, MS, NMOSD, GBS, and CIDP). The mRS was scored as follows: 0, no symptoms; 1, no significant disability; 2, slight disability; 3, moderate disability; 4, moderately severe disability; 5, severe disability; and 6, dead [10]. The BI, developed in 1965, is currently widely used as a simple method to assess the activities of daily living for various diseases. The rating scale is 0, 5, 10, and 15 points [11].

2.4 | Ethics

The protocol conformed to the provisions of the Declaration of Helsinki [12]. This study was approved by the ethics committee of all 13 participating hospitals. Written informed consent was obtained from all patients or their guardians in the case of patients aged <20 years.

TABLE 1 Rate of receiving plasmapheresis and rate of inclusion in the 12 hospitals participating in the study

	Total	MG	MS	NMOSD	CIDP	GBS	Others
Number of patients enrolled in this study[a]	207	82	29	24	11	4	57
Number of patients received plasmapheresis	463	95	161	60	36	8	103
Number of inpatients with autoimmune neurological diseases	1910	369	664	200	331	58	288
Rate of receiving plasmapheresis[b] (%)	24.2	25.7	24.2	30.0	10.9	13.8	35.8
Rate of inclusion in this study[c] (%)	44.7	86.3	18.0	40.0	30.6	50.0	55.3

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; MG, myasthenia gravis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders.

[a]The total number of patients included in this analysis was 207, rather than the total of 210 patients enrolled in the study since one of the 13 hospitals did not respond to the survey.

[b]Rate of receiving plasmapheresis = Number of patients receiving plasmapheresis/number of inpatients with autoimmune neurological diseases.

[c]Rate of inclusion in this study = Number of patients enrolled in this study/number of patients who received plasmapheresis.

2.5 | Data management and statistics

Data management and statistical analyses were performed using Mebix, Inc., as the independent platform. A safety assessment was conducted with patients who received plasmapheresis at least once during the study period. Side effects were classified according to MedDRA/J version 22.0. For all other evaluations, the full analysis set (FAS) was established for analysis. The FAS was defined as patients who underwent plasmapheresis. For clinical outcome assessment, mRS and BI scores before and after plasmapheresis were compared using the Wilcoxon matched-pair signed-rank test. Statistical analyses were performed using SAS software (version 9.4; SAS Institute, Inc.). Statistical significance was set at $p < 0.05$.

3 | RESULTS

3.1 | Patients

A total of 210 patients were enrolled in this study between May 2017 and March 2019. No patient was excluded before receiving plasmapheresis. All patient data were included in the safety assessment. No patient was excluded. The data of all patients were defined as the FAS. Fifty patients were excluded from the clinical outcome assessments due to the lack of data before or after plasmapheresis. Consequently, data from 160 patients were used for the clinical outcome assessment.

3.2 | Rate of receiving plasmapheresis and rate of inclusion

The rate of receiving plasmapheresis and the rate of inclusion for each disease in the 12 hospitals that responded to the additional survey are shown in Table 1. Approximately, one-quarter of inpatients diagnosed with autoimmune neurological diseases were treated with plasmapheresis. Approximately half of the patients were ultimately enrolled in this study.

3.3 | Diagnosis and demographic data

The diagnoses of the 210 patients are presented in Table 2. The most frequent disease among patients treated with plasmapheresis was MG, with 82 patients. The next most frequent disease was autoimmune encephalitis/encephalopathy, with 40 patients. This was followed by MS, NMOSD, CIDP, and GBS with 30, 24, 11, and four patients, respectively.

The demographic data of the 210 patients are summarized in Table 3. Females were predominant, representing 151 patients (71.9%), compared to only 59 men (28.1%). The average age was 47.1 years, median was 48 years, with a range from15 to 83 years. Forty-nine of the 210 patients presented with their first disease onset. The other 148 patients presented with relapse. In addition, plasmapheresis was performed at regular intervals as maintenance therapy in 13 patients. This was irrespective of the clinical symptoms of the disease.

3.4 | Procedure of plasmapheresis-patients

IAPP was the most frequently performed plasmapheresis modality during the study period (Table 4). With respect to disease, MG was mainly treated with PE or IAPP at a rate of 53.7% and 41.5%, respectively; MS was mainly treated with IAPP (56.7%), and NMOSD was primarily treated with IAPP (83.3%). Regarding the frequency of

TABLE 2 Diagnoses of the 210 patients

Diagnosis	Number of patients for the full analysis set (percentage of total patients)	Number of patients for outcome assessment (percentage of total patients)
Gross[a]	210 (100.0)	160 (100.0)
MG	82 (39.0)	73 (45.6)
MS	30 (14.3)	27 (16.9)
NMOSD	24 (11.4)	18 (11.3)
CIDP	11 (5.2)	7 (4.4)
GBS	4 (1.9)	4 (2.5)
Others	59 (28.1)	31 (19.4)
Autoimmune encephalitis[b]/encephalopathy	40 (19.0)	17 (10.6)
Hashimoto encephalopathy	4 (1.9)	3 (1.9)
Anti-MOG antibody-related demyelinating diseases	4 (1.9)	4 (2.5)
Lambert–Eaton syndrome	3 (1.4)	3 (1.9)
Isaacs syndrome	1 (0.5)	1 (0.6)
Stiff-person syndrome	1 (0.5)	0 (0.0)
Systemic lupus erythematosus myelitis	1 (0.5)	0 (0.0)
IgM-type ganglioside antibody neuropathy	1 (0.5)	1 (0.6)
Autoimmune cerebellar ataxia	1 (0.5)	1 (0.6)
Myelitis	1 (0.5)	0 (0.0)
Others	2 (1.0)	1 (0.6)

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain–Barré syndrome; MG, myasthenia gravis; MOG, myelin oligodendrocyte glycoprotein; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders.

[a]Twenty-nine of 210 patients were re-enrolled.

[b]Autoimmune encephalitis includes NMDAR encephalitis ($n = 3$) and limbic encephalitis ($n = 2$).

plasmapheresis, the mean, standard deviation, median, minimum, and maximum number of treatments per patient were 4.2, 2.4, 5, 1, and 14, respectively. However, the mean number of treatments varied depending on the disease. MS had the highest mean number of treatments performed, followed by NMOSD, CIDP, GBS, and MG with 6.3, 4.7, 4.5, 3.3, and 2.6, respectively. After aggregating the rationale for introducing plasmapheresis, it was shown that plasmapheresis was most frequently performed in cases of relapse, resistance to previous therapy, and acute exacerbation. From the patient perspective, the reasons for the completion or termination of plasmapheresis were improvement in symptoms, suspension of progression, and insufficient/no effect for 177, 13, and 13 patients, respectively.

3.5 | Procedure of plasmapheresis-treatments

A total of 887 treatments were performed in 210 patients, with PE, DFPP, and IAPP accounting for 213, 54, and 620 of the treatments, respectively (Table 5). The treatment times were comparable among the three modalities, with mean values of Gross, PE, DFPP, and IAPP of 130.9, 135.4, 121.4, and 130.3 min, respectively. Regarding the replacement fluid, 5% albumin solution was more commonly used as the replacement fluid for both PE and DFPP in 159 and 43 treatments, respectively, compared to the use of FFP in four and zero treatments, respectively. Regarding the anticoagulants, heparin and nafamostat mesylate were commonly administered in 512 and 353 treatments, respectively, whereas sodium citrate was used in only two treatments.

3.6 | Vascular access

Information on vascular access is shown in Table 5. A total of 565 treatments were performed using only needles, 246 treatments were performed using only catheter blood accesses, 44 treatments were performed using both a needle, and catheter and no information on vascular access was provided for 32 treatments. Of the total

TABLE 3 Demographic data of the included patients

	Gross	MG	MS	NMOSD	CIDP	GBS	Others
Number of patients	210	82	30	24	11	4	59
Gender, *n* (%)							
Male	59 (28.1)	28 (34.1)	8 (26.7)	4 (16.7)	7 (63.6)	2 (50.0)	10 (16.9)
Female	151 (71.9)	54 (65.9)	22 (73.3)	20 (83.3)	4 (36.4)	2 (50.0)	49 (83.1)
Age (years)							
Mean ± SD	47.1 ± 16.7	53.6 ± 15.2	44.6 ± 10.0	53.4 ± 12.9	51.2 ± 15.3	54.5 ± 14.3	35.5 ± 17.1
Median	48.0	50.5	45.5	57.5	45.0	58.0	29.0
Min, Max	15, 83	22, 83	16, 62	26, 70	29, 74	35, 67	15, 73
Body weight (kg)							
Mean ± SD	59.13 ± 14.70	62.16 ± 15.91	56.43 ± 12.50	58.00 ± 13.96	68.94 ± 21.51	61.50 ± 5.80	54.76 ± 11.52
Median	55.90	60.50	54.50	52.75	65.00	59.50	53.20
Min, Max	32.9, 136.0	32.9, 136.0	40.0, 90.8	36.7, 89.0	45.6, 117.0	57.0, 70.0	41.0, 93.4
Inpatient or outpatient, *n* (%)							
Inpatients	204 (97.1)	82 (100.0)	29 (96.7)	21 (87.5)	9 (81.8)	4 (100.0)	59 (100.0)
Outpatients	6 (2.9)	0 (0.0)	1 (3.3)	3 (12.5)	2 (18.2)	0 (0.0)	0 (0.0)
First onset, relapse, or maintenance, *n* (%)							
First onset	49 (23.3)	23 (28.0)	1 (3.3)	6 (25.0)	1 (9.1)	4 (100.0)	14 (23.7)
Relapse	148 (70.5)	57 (69.5)	26 (86.7)	15 (62.5)	5 (45.5)	0 (0.0)	45 (76.3)
Maintenance[a]	13 (6.2)	2 (2.4)	3 (10.0)	3 (12.5)	5 (45.5)	0 (0.0)	0 (0.0)
Plasmapheresis treatment history within the last three months, *n* (%)							
None	134 (63.8)	47 (57.3)	27 (90.0)	18 (75.0)	6 (54.5)	2 (50.0)	34 (57.6)
Yes	76 (36.2)	35 (42.7)	3 (10.0)	6 (25.0)	5 (45.5)	2 (50.0)	25 (42.4)
Unknown	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain–Barré syndrome; MG, myasthenia gravis; MS, multiple sclerosis; *n*, number of patients; NMOSD, neuromyelitis optica spectrum disorders; SD, standard deviation.
[a]Cases in which plasmapheresis is regularly performed without exacerbation of clinical symptoms of the disease.

855 treatments for which data were available, 541 (63.3%) were performed with peripheral blood access only. The major peripheral blood access site was the forearm vein, followed by the brachial vein with 485 and 37 treatments, respectively. Regarding catheter blood access, 172 (20.1%) and 67 (7.8%) catheters were placed in the internal jugular vein or femoral vein. Regarding the needle size, the most commonly selected sizes were 17 and 12 for peripheral and catheter blood access, respectively.

3.7 | Safety (side effects due to plasmapheresis)

Table 6 presents the side effects during the study period. No serious side effects due to plasmapheresis were observed. However, non-serious side effects were observed in 10 out of 210 patients (4.8%) and 11 out of 887 treatments (1.2%). The non-serious side effects included nausea (1.9%), vomiting (0.5%), device-related infection (0.5%), hemolysis (0.5%), dyspnea (0.5%), and fibrinogen decrease (0.5%). There were four events of nausea, three of which occurred in the same patient who was re-enrolled in this study. Only one plasmapheresis treatment was discontinued due to a side effect, which was judged to be a catheter-related infection.

3.8 | Clinical outcome assessment

Among the 210 patients, 160 were evaluated based on mRS and BI scores. As shown in Table 7, 14 (8.8%) patients showed improvement of two points or more, and 84 (52.5%) showed a one-point improvement in the mRS after plasmapheresis. A statistically significant difference was noted between the mRS scores before and after plasmapheresis in Gross, MG, MS, and NMOSD. No significant difference was observed in CIDP. As shown in

TABLE 4 Procedure of plasmapheresis-patients

	Gross	MG	MS	NMOSD	CIDP	GBS	Others
Number of patients	210	82	30	24	11	4	59
Plasmapheresis, *n* (%)							
PE	68 (32.4)	44 (53.7)	5 (16.7)	1 (4.2)	5 (45.5)	0 (0.0)	13 (22.0)
DFPP	8 (3.8)	1 (1.2)	2 (6.7)	2 (8.3)	2 (18.2)	0 (0.0)	1 (1.7)
IAPP	124 (59.0)	34 (41.5)	17 (56.7)	20 (83.3)	4 (36.4)	4 (100.0)	45 (76.3)
PE + IAPP	4 (1.9)	1 (1.2)	3 (10.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
PE + DFPP	5 (2.4)	2 (2.4)	2 (6.7)	1 (4.2)	0 (0.0)	0 (0.0)	0 (0.0)
DFPP + IAPP	1 (0.5)	0 (0.0)	1 (3.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Number of treatments per patient							
Mean ± SD	4.2 ± 2.4	2.6 ± 2.5	6.3 ± 1.8	4.7 ± 1.5	4.5 ± 2.0	3.3 ± 0.5	5.3 ± 1.6
Median	5	1	7	4	5	3	6
Min, Max	1, 14	1, 14	2, 11	3, 7	1, 7	3, 4	1, 7
Reason to induce plasmapheresis,[a] *n*							
Relapse	111	42	18	12	4	0	35
Resistant to previous therapy	90	14	25	15	6	0	30
Acute exacerbation	41	17	2	9	2	4	7
Severe case	12	4	1	0	1	4	2
Induction of initial remission	10	5	0	1	0	0	4
Crisis	7	7	-	-	-	-	-
Thymectomy related	6	6	-	-	-	-	-
Diagnostic therapy	2	2	0	0	0	0	2
Coincidence of PML	1	1	0	0	0	0	1
Others	8	4	2	1	1	0	0
Rationale to withdraw plasmapheresis,[a] *n*							
Improved	177	77	23	21	8	0	48
Suspension of progression	13	2	2	2	1	1	5
Insufficient or no effect	13	1	5	1	2	0	4
Others	6	1	1	1	1	0	2

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; DFPP, double filtration plasmapheresis; GBS, Guillain-Barré syndrome; IAPP, immunoadsorption plasmapheresis; MG, myasthenia gravis; MS, multiple sclerosis; *n*, number of patients; NMOSD, neuromyelitis optica spectrum disorders; PE, plasma exchange; PML, progressive multifocal leukoencephalopathy; SD, standard deviation.

[a]Multiple selections for the reasons were allowed to check the case report forms.

Table 8, the BI scores showed statistically significant improvement after plasmapheresis in Gross, MG, MS, and NMOSD. However, no significant improvement was noted in CIDP.

4 | DISCUSSION

This study shows that in Japan, plasmapheresis can be applied to various neurological disorders as a recognition of immunological involvement. The most frequent disease treated with plasmapheresis was MG, followed by autoimmune encephalitis/encephalopathy, MS, NMOSD, CIDP, and GBS. This finding is consistent with a previous report from the International Apheresis Registry [13]. This report showed that approximately 20% of all registered patients were diagnosed with neurological diseases. The majority of them were MG, except for autoimmune encephalitis/encephalopathy, in which plasmapheresis has been recognized as effective. Plasmapheresis is most frequently applied in relapse cases, resistance to conventional therapies, or acute exacerbation of neurological diseases. Consequently, more than 60% of the patients showed improvement, and no deterioration of condition was observed after treatment. The improvement of symptoms may not be attributed only to plasmapheresis.

TABLE 5 Procedure of plasmapheresis-treatments

	Gross[a]	PE	DFPP	IAPP
Number of treatments	**887**	**213**	**54**	**620**
Treatment time (min)				
N	852	197	52	603
Mean ± SD	130.9 ± 32.6	135.4 ± 28.3	121.4 ± 19.8	130.3 ± 34.6
Processed plasma volume (mL)				
N	867	200	53	614
Mean ± SD	1729.2 ± 601.1	2509.3 ± 742.9	1687.5 ± 350.8	1478.7 ± 243.7
Blood flow rate (mL/min)				
N	857	198	52	607
Mean ± SD	57.6 ± 24.8	70.3 ± 20.7	52.1 ± 14.6	54.0 ± 25.4
Plasma filtration flow rate (mL/min)				
N	850	192	51	607
Mean ± SD	15.2 ± 5.2	20.1 ± 5.0	15.7 ± 3.4	13.7 ± 4.3
Wasted plasma flow rate (mL/min)				
N	-	-	43	-
Mean ± SD	-	-	4.240 ± 2.424	-
Replacement solution volume (mL)				
5% albumin				
N	202	159	43	-
Mean ± SD	1913.2 ± 771.8	2234.0 ± 503.0	727.0 ± 262.4	-
Fresh frozen plasma				
N	4	4	0	-
Mean ± SD	2880.0 ± 0	2880.0 ± 0	-	-
Anticoagulants, *n*				
Heparin	512			
Nafamostat mesylate	353			
Sodium citrate	2			
Low-molecular-weight heparin	1			
Unknown	19			
Vascular access methods, *n*				
Catheter indwelling	246			
Internal jugular vein	172			
Femoral vein	67			
Unknown	7			
Needle puncture	565			
Peripheral vein	541			
Forearm vein	485			
Brachial vein	37			
External jugular vein	13			
Others	6			
Central vein	4			
Femoral vein	4			

(Continues)

TABLE 5 (Continued)

	Gross[a]	PE	DFPP	IAPP
Number of treatments	**887**	**213**	**54**	**620**
Both peripheral vein and central vein	8			
Forearm vein and femoral vein	8			
Unknown	12			
Both catheter indwelling and needle puncture	44			
Internal jugular vein	39			
Femoral vein	1			
Unknown	4			
Unknown[b]	32			
Vascular access size, *n*				
Catheter	290			
8 French	77			
11 French	74			
12 French	133			
13 French	6			
Blood-collecting needle	566			
16 Gauge	1			
17 Gauge	319			
18 Gauge	224			
20 Gauge	22			
Blood-returning needle	608			
17 Gauge	361			
18 Gauge	19			
20 Gauge	228			

Abbreviations: DFPP, double filtration plasmapheresis; IAPP, immunoadsorption plasmapheresis; *n*, number of treatments; *N*, number of treatments available for data analysis; PE, plasma exchange; SD, standard deviation.

[a]Gross represents the sum of PE, DFPP, and IAPP.

[b]No information was available on which type of blood access was applied.

It could be attributed to concomitant medication instead. However, plasmapheresis could surely exert at least an adjunct effect and is expected to exert an immediate improvement of symptoms. This is because it removes virulence factors directly from the blood. Liu et al. [14] reported that plasmapheresis showed better short-term clinical effectiveness than an immunoglobulin transfusion in patients with MG. Furthermore, various studies have demonstrated the usefulness of plasmapheresis for autoimmune neurological diseases, including MG [14, 15], MS [16–19], NMOSD [18, 20, 21], and autoimmune encephalitis/encephalopathy [16, 22, 23].

IAPP was identified as the most frequently selected plasmapheresis modality in this study. This might be because IAPP has no risk of infection due to the administration of blood products. The immunoadsorption column used in the hospitals participating in this study was almost exclusively Immusorba TR (Asahi Kasei Medical Co., Ltd.). It selectively adsorbs IgG1 and IgG3 subclasses but has lower adsorption for other IgG subclasses [24, 25]. Therefore, IAPP using Immusorba TR would be a better choice when the patient's autoantibody belongs to IgG1 and IgG3. However, PE would be more appropriate if the autoantibody is another immunoglobulin such as IgG4. Anti-acetylcholine receptor (anti-AChR) antibodies, which are the major specific autoantibodies of MG, are usually classified as IgG1 and IgG3 with complement activation ability [26, 27]. Although, certain patients with MG have anti-muscle-specific tyrosine kinase (anti-MuSK) antibodies. These are usually classified as IgG4 without complement activation ability [26, 27]. Therefore, IAPP using Immusorba TR might be preferable for application in MG patients with anti-AChR antibodies. PE might be preferable for MG patients with anti-MuSK antibodies or without information on autoantibody subclasses. Furthermore, the major specific

TABLE 6 Safety (side effects due to plasmapheresis)

Total		Number of patients 210	Frequency of side effects (% patients) -	Number of treatments 887	Frequency of side effects (% treatments) -
Number of side effects		10	4.8	11	1.2
Serious		0	0	0	0
Non-serious		10	4.8	11	1.2
SOC	PT				
Infections and infestations		1	0.5	1	0.1
	Device-related infection	1	0.5	1	0.1
Blood and lymphatic system disorders		1	0.5	1	0.1
	Hemolysis	1	0.5	1	0.1
Nervous system disorders		1	0.5	1	0.1
	Seizure	1	0.5	1	0.1
Respiratory, thoracic, and mediastinal disorders		1	0.5	1	0.1
	Dyspnea	1	0.5	1	0.1
Gastrointestinal disorders		5	2.4	6	0.7
	Nausea	4[a]	1.9	5	0.6
	Vomiting	1	0.5	1	0.1
Investigations		1	0.5	1	0.1
	Fibrinogen decreased	1	0.5	1	0.1

Abbreviations: PT, preferred term; SOC, system organ class.
[a]There were four events of nausea, three of which occurred in the same patient.

autoantibodies of NMOSD are anti-aquaporin-4 (AQP4) antibodies, which are usually classified as IgG1 [28]. Therefore, IAPP would be preferable for application in NMOSD patients.

The average number of treatments for MG patients was 2.6, which was lower than that for other diseases. A possible reason for this lower treatment number is the bias from one hospital. This hospital has a specific policy of applying IAPP or PE once or twice in the early onset stage of MG before prescribing medication. In other hospitals, plasmapheresis for MG was performed as often as for other diseases (data not shown). According to reports from other groups, PE was performed five times per patient for 187 patients with autoimmune neurological disease [7], a mean of 3.9 times for 26 patients with MG [29], and a mean of 7.39 times for 46 patients with severe acute relapses of MS. [30] These frequencies were comparable to the results of this study, except for the MG data from one hospital.

This study further showed that many plasmapheresis procedures were performed with blood access obtained from peripheral vessels, such as the forearm and brachial veins, instead of indwelling catheters. One problem with plasmapheresis is the difficulty of vascular access to obtain sufficient blood flow for extracorporeal blood circulation [13, 31]. An indwelling catheter is thought to be the major vascular access for plasmapheresis. However, this requires a skillful procedure for physicians and physical restriction for patients. It is also associated with a risk of developing catheter infections [31]. In fact, one case of catheter-related infection was recorded in this study. Accessing the peripheral vessels enables the progression of plasmapheresis to outpatients and may help to reduce the burden on patients associated with hospitalization. In the future, vascular access via the peripheral vessels for plasmapheresis may become standard, although it requires the selection of proper vessels.

In this study, the frequency of all side effects was less than 2% in 887 treatments, which is lower than in previous reports [13, 32]. One possible reason could be the difference in the range of safety information collected among the various studies. This study restricted the

TABLE 7 Clinical response evaluated by the modified Rankin scale (mRS)

	Gross[a]		MG		MS		NMOSD		CIDP		GBS		Others	
Number of patients (%)	160		73		27		18		7		4		31	
2 points or more improvement	14	(8.8)	6	(8.2)	4	(14.8)	1	(5.6)	0	(0.0)	0	(0.0)	3	(9.7)
1 point improvement	84	(52.5)	53	(72.6)	9	(33.3)	7	(38.9)	3	(42.9)	0	(0.0)	12	(38.7)
No difference	62	(38.8)	14	(19.2)	14	(51.9)	10	(55.6)	4	(57.1)	4	(100.0)	16	(51.6)
Deterioration	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
mRS score[b]	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
0	0	10	0	5	0	2	0	1	0	1	0	0	0	1
1	13	59	8	46	1	4	1	2	1	1	0	0	2	6
2	72	46	46	16	8	10	4	5	3	3	0	0	11	12
3	37	21	13	4	11	7	5	5	2	1	0	0	6	4
4	24	15	3	2	7	4	5	2	1	1	0	0	8	6
5	14	9	3	0	0	0	3	3	0	0	4	4	4	2
6	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Median	2	2	2	1	3	2	3	3	2	2	5	5	3	2
p value[c]	<0.0001		<0.0001		0.0002		0.0078		0.2500		-		<0.0001	

Abbreviations: CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; MG, myasthenia gravis; mRS, modified Rankin Scale; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders.

[a]Gross includes MG, MS, NMOSD, CIDP, GBS, and others.

[b]mRS scoring interpretation: 0, no symptoms; 1, no significant disability, able to carry out all usual activities, despite some symptoms; 2, Slight disability, able to look after own affairs without assistance, but unable to carry out all previous activities; 3, Moderate disability, requires some help, but able to walk unassisted; 4, Moderately severe disability, unable to attend to own bodily needs without assistance, and unable to walk unassisted; 5, severe disability, requiring constant nursing care and attention, bedridden, incontinent; 6, Dead.

[c]Wilcoxon signed-rank test.

TABLE 8 Clinical response evaluated by the Barthel Index

	Gross		MG		MS		NMOSD		CIDP		GBS		Others	
Number of patients	160		73		27		18		7		4		31	
BI score	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After	Before	After
Median	95	100	100	100	90	95	85	95	95	100	0	0	90	95
Min, Max	0, 100	0, 100	0, 100	60, 100	70, 100	75, 100	5, 100	10, 100	65, 100	70, 100	0, 0	0, 0	0, 100	5, 100
p value[a]	<0.0001		<0.0001		0.0002		0.0010		0.5000		-		0.0001	

Abbreviations: BI, Barthel Index; CIDP, chronic inflammatory demyelinating polyneuropathy; GBS, Guillain-Barré syndrome; MG, myasthenia gravis; MS, multiple sclerosis; NMOSD, neuromyelitis optica spectrum disorders.

[a]Wilcoxon signed-rank test.

recording of side effects associated with plasmapheresis. Previous studies might have recorded the events without restriction of the relation to plasmapheresis. Another possible reason is the difference in anticoagulant selection. In the International Apheresis Registry of 2007, many of the side effects and complications of paresthesia, citrate-induced reactions, allergic reactions, hypertension, and hypocalcemia could be related to the use of sodium citrate as an anticoagulant [13]. Only a few cases in this study used citrate.

One interesting finding of this study was that some patients regularly underwent plasmapheresis as maintenance therapy, irrespective of the clinical symptoms of the patient's disease. Plasmapheresis removes pathogenic molecules released into the blood and is not a definitive treatment for autoimmune neurological diseases. However, the removal of autoantibodies by maintenance plasmapheresis may prevent deterioration of the patient's condition [33]. Further studies are required to investigate the type of patients and the most suitable frequency for maintenance plasmapheresis treatments.

Another interesting finding was that many patients with diseases not covered by public insurance, such as autoimmune encephalitis or encephalopathy, were enrolled and responded significantly to plasmapheresis and the currently approved diseases. Appropriate randomized controlled trials would be ideal even in such disorders. This is often difficult because of the rarity, severity, and acute course of the illness. Many studies have reported the usefulness of plasmapheresis for autoimmune encephalitis and encephalopathy [16, 22]. Therefore, we expect that real-world data will lead to the expansion of public insurance coverage for these conditions.

4.1 | Limitations

This study had several limitations. This was a one-armed observational study involving a wide variety of neurological diseases. Biases of the types of diseases could exist because of the specialty of each hospital. Moreover, selection bias could also exist as some patients who had undergone plasmapheresis were not registered. In addition, the efficacy could not be determined since treatments other than plasmapheresis, including medication, were not restricted during the study period.

5 | CONCLUSION

This study highlights the latest status of plasmapheresis in autoimmune neurological diseases in Japan. Plasmapheresis may be considered an efficient therapy for autoimmune

neurological diseases such as myasthenia gravis, multiple sclerosis, neuromyelitis optica spectrum disorders, chronic inflammatory demyelinating polyneuropathy, and Guillain–Barré syndrome, with a low frequency of adverse events.

ACKNOWLEDGMENTS

This study was financially supported by Asahi Kasei Medical Co., Ltd. The authors would like to thank the J-POPPS (Japan-Plasmapheresis Outcome and Practice Patterns Study) group for their contribution to the study: Dr Hiroshi Takashima (Kagoshima University Hospital), Kimiaki Utsugisawa (General Hanamaki Hospital), Yuji Takahashi (National Center of Neurology and Psychiatry), Kyoichi Nomura (Saitama Medical Center), Susumu Kusunoki (Kindai University Hospital), Masaaki Niino (Hokkaido Medical Center), Kazumasa Yokoyama (Juntendo University Hospital), Shugo Suwazono (Okinawa National Hospital), Osamu Watanabe (Kagoshima City Hospital), Masahiro Mori (Chiba University Hospital), Hiroo Yoshikawa (Hyogo College of Medicine Hospital), and Yuji Nakatsuji (Toyama University Hospital).

CONFLICTS OF INTEREST

Mana Kameyama is an employee of Asahi Kasei Medical Co., Ltd. The remaining authors declare no conflict of interest.

ORCID

Youwei Lin https://orcid.org/0000-0001-7561-5577

REFERENCES

1. Ginestal-López RC. Immunotherapy for neurological diseases, present and future. Farm Hosp. 2018;42(6):251–60. https://doi.org/10.7399/fh.11031
2. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I, et al. International consensus guidance for management of myasthenia gravis: executive summary. Neurol. 2016;87(4):419–25. https://doi.org/10.1212/WNL.0000000000002790
3. Hauser SL, Cree BAC. Treatment of multiple sclerosis: a review. Am J Med. 2020;133(12):1380–90. https://doi.org/10.1016/j.amjmed.2020.05.049
4. Martin R, Sospedra M, Rosito M, Engelhardt B. Current multiple sclerosis treatments have improved our understanding of MS autoimmune pathogenesis. Eur J Immunol. 2016;46(9):2078–90. https://doi.org/10.1002/eji.201646485
5. Cortese I, Cornblath DR. Therapeutic plasma exchange in neurology: 2012. J Clin Apher. 2013;28(1):16–9. https://doi.org/10.1002/jca.21266
6. von Geldern G, McPharlin T, Becker K. Immune mediated diseases and immune modulation in the neurocritical care unit. Neurotherapeutics. 2012;1:99–123. https://doi.org/10.1007/s13311-011-0096-3
7. Nieto-Aristizábal I, Vivas ÁJ, Ruiz-Montaño P, Aragón CC, Posso-Osorio I, Quiñones J, et al. Therapeutic plasma exchange as a treatment for autoimmune neurological disease. Autoimmune Dis. 2020;2020:3484659. https://doi.org/10.1155/2020/3484659
8. Rolfes L, Pfeuffer S, Ruck T, Melzer N, Pawlitzki M, Heming M, et al. Therapeutic apheresis in acute relapsing multiple sclerosis: current evidence and unmet needs- a systematic review. J Clin Med. 2019;8(10):1623. https://doi.org/10.3390/jcm8101623
9. Padmanabhan A, Connelly-Smith L, Aqui N, Balogun RA, Klingel R, Meyer E, et al. Guidelines on the use of therapeutic apheresis in clinical practice - evidence-based approach from the writing committee of the American society for apheresis: the eighth special issue. J Clin Apher. 2019;3:171–354. https://doi.org/10.1002/jca.21705
10. Broderick JP, Adeoye O, Elm J. Evolution of the modified Rankin scale and its use in future stroke trials. Stroke. 2017;48(7):2007–12. https://doi.org/10.1161/STROKEAHA.117.017866
11. Mahoney FI, Barthel DW. Functional evaluation: the Barthel index. Md State Med J. 1965;14:61–5.
12. World Medical Association. World medical association declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA. 2013;310(20):2191–4. https://doi.org/10.1001/jama.2013.281053
13. Malchesky PS, Koo AP, Skibinski CI, Hadsell AT, Rybicki LA. Apheresis technologies and clinical applications: the 2007 international apheresis registry. Ther Apher Dial. 2010;14(1):52–73. https://doi.org/10.1111/j.1744-9987.2009.00716.x
14. Liu JF, Wang WX, Xue J, Zhao CB, You HZ, Lu JH, et al. Comparing the autoantibody levels and clinical efficacy of double filtration plasmapheresis, immunoadsorption, and intravenous immunoglobulin for the treatment of late-onset myasthenia gravis. Ther Apher Dial. 2010;14(2):153–60. https://doi.org/10.1111/j.1744-9987.2009.00751.x
15. Barth D, Nabavi Nouri M, Ng E, Nwe P, Bril V. Comparison of IVIg and PLEX in patients with myasthenia gravis. Neurol. 2011;76(23):2017–23. https://doi.org/10.1212/WNL.0b013e31821e5505
16. Moser T, Harutyunyan G, Karamyan A, Otto F, Bacher C, Chroust V, et al. Therapeutic plasma exchange in multiple sclerosis and autoimmune encephalitis: a comparative study of indication, efficacy and safety. Brain Sci. 2019;9(10):267. https://doi.org/10.3390/brainsci9100267
17. Dorst J, Fangerau T, Taranu D, Eichele P, Dreyhaupt J, Michels S, et al. Safety and efficacy of immunoadsorption versus plasma exchange in steroid-refractory relapse of multiple sclerosis and clinically isolated syndrome: a randomised, parallel-group, controlled trial. EClin Med. 2019;16:98–106. https://doi.org/10.1016/j.eclinm.2019.10.017
18. Lipphardt M, Wallbach M, Koziolek MJ. Plasma exchange or immunoadsorption in demyelinating diseases: a meta-analysis. J Clin Med. 2020;9(5):1597. https://doi.org/10.3390/jcm9051597
19. Schimrigk S, Faiss J, Köhler W, Günther A, Harms L, Kraft A, et al. Escalation therapy of steroid refractory multiple sclerosis relapse with tryptophan immunoadsorption - observational multicenter study with 147 patients. Eur Neurol. 2016;75(5–6):300–6. https://doi.org/10.1159/000447059
20. Abboud H, Petrak A, Mealy M, Sasidharan S, Siddique L, Levy M. Treatment of acute relapses in neuromyelitis optica: steroids alone versus steroids plus plasma exchange. Mult Scler. 2016;2:185–92. https://doi.org/10.1177/1352458515581438

21. Kleiter I, Gahlen A, Borisow N, Fischer K, Wernecke KD, Hellwig K, et al. Apheresis therapies for NMOSD attacks: a retrospective study of 207 therapeutic interventions. Neurol Neuroimmunol Neuroinflamm. 2018;5(6):e504. https://doi.org/10.1212/NXI.0000000000000504
22. Heine J, Ly LT, Lieker I, Slowinski T, Finke C, Prüss H, et al. Immunoadsorption or plasma exchange in the treatment of autoimmune encephalitis: a pilot study. J Neurol. 2016;263(12):2395–402. https://doi.org/10.1007/s00415-016-8277-y
23. Dogan Onugoren M, Golombeck KS, Bien C, Abu-Tair M, Brand M, Bulla-Hellwig M, et al. Immunoadsorption therapy for autoimmune encephalitides. Neurol Neuroimmunol Neuroinflamm. 2016;3(2):e207. https://doi.org/10.1212/NXI.0000000000000207
24. Yasuda T, Mikami T, Kawase Y. Efficacy of tryptophan immunoadsorption plasmapheresis for neuromyelitis optica in two cases. Ther Apher Dial. 2015;19(4):411–2. https://doi.org/10.1111/1744-9987
25. Yoshikawa T, Baba A, Akaishi M, Wakabayashi Y, Monkawa T, Kitakaze M, et al. Immunoadsorption therapy for dilated cardiomyopathy using tryptophan column- a prospective, multicenter, randomized, within-patient and parallel-group comparative study to evaluate efficacy and safety. J Clin Apher. 2016;6:535–44. https://doi.org/10.1002/jca.21446
26. Binks S, Vincent A, Palace J. Myasthenia gravis: a clinical-immunological update. J Neurol. 2016;263(4):826–34. https://doi.org/10.1007/s00415-015-7963-5
27. Meriggioli MN, Sanders DB. Autoimmune myasthenia gravis: emerging clinical and biological heterogeneity. Lancet Neurol. 2009;8:475–90. https://doi.org/10.1016/S1474-4422(09)70063-8
28. Graber DJ, Levy M, Kerr D, Wade WF. Neuromyelitis optica pathogenesis and aquaporin 4. J Neuroinflammation. 2008;5:22. doi.org/10.1186/1742-2094-5-22
29. Carandina-Maffeis R, Nucci A, Marques JF Jr, Roveri RG, Pfeilsticker BH, Garibaldi SG, et al. Plasmapheresis in the treatment of myasthenia gravis: retrospective study of 26 patients. Arq Neuropsiquiatr. 2004;62(2B):391–5. https://doi.org/10.1590/s0004-282x2004000300003
30. Correia I, Ribeiro JJ, Isidoro L, Batista S, Nunes C, Macário C, et al. Plasma exchange in severe acute relapses of multiple sclerosis - results from a Portuguese cohort. Mult Scler-Relat Disord. 2018;19:148–52. https://doi.org/10.1016/j.msard.2017.12.001
31. Stegmayr B, Wikdahl AM. Access in therapeutic apheresis. Ther Apher Dial. 2003;7(2):209–14. https://doi.org/10.1046/j.1526-0968.2003.00035.x
32. Ishihara T, Inoue S, Takagi Y, Shimomura T, Sagami Y, Katayama S, et al. Adverse events in therapeutic apheresis: a single center survey of various therapies. Ther Apher Dial. 2010;14(6):589–95. https://doi.org/10.1111/j.1744-9987.2010.00832.x
33. Miyamoto K, Kusunoki S. Intermittent plasmapheresis prevents recurrence in neuromyelitis optica. Ther Apher Dial. 2009;13(6):505–8. https://doi.org/10.1111/j.1744-9987.2009.00780.x

How to cite this article: Lin Y, Oji S, Miyamoto K, Narita T, Kameyama M, Matsuo H. Real-world application of plasmapheresis for neurological disease: Results from the Japan-Plasmapheresis Outcome and Practice Patterns Study. Ther Apher Dial. 2023;27(1):123–35. https://doi.org/10.1111/1744-9987.13906