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Clinical Efficacy of Plasmapheresis in Patients with Neuromyelitis Optica Spectrum Disorder and Effects on Circulating Anti-Aquaporin-4 Antibody Levels

Su-Hyun Kim, Woojun Kim, So-Young Huh, Kyue Yim Lee, In Ja Jung, Ho Jin Kim

Department of Neurology, Research Institute and Hospital of National Cancer Center, Goyang, Korea

Background and Purpose Although plasmapheresis is becoming standard practice as a rescue therapy for neuromyelitis optica (NMO), evidence for the therapeutic efficacy of plasmapheresis is limited, and the effect of plasmapheresis on anti-aquaporin-4 (AQP4) levels in patients with NMO has not been reported. Here, our objective was to evaluate the clinical efficacy of therapeutic plasmapheresis and its effect on anti-AQP4 antibody levels in patients with NMO spectrum disorder (NMOSD).

Methods We retrospectively reviewed the medical records of 15 patients with NMOSD who had 18 acute attacks and received plasmapheresis because they did not respond to high-dose intravenous methylprednisolone (IVMP) therapy. Anti-AQP4 antibodies were measured before and after plasmapheresis. The primary outcomes were functional improvements immediately and 6 months after plasmapheresis, and the secondary outcome was the change in anti-AQP4 antibody serum levels following plasmapheresis.

Results Plasmapheresis following IVMP therapy led to significant improvement in 50% of the 18 attacks in 15 patients immediately after the procedure was completed, and in 78% (14 attacks) after 6 months. Plasmapheresis was generally well tolerated in all patients. Anti-AQP4 antibody serum levels declined significantly following plasmapheresis, to a mean of 15% of the preplasmapheresis levels. Lower scores on the visual outcome scale recorded before an attack were associated with significant immediate improvement upon the completion of plasmapheresis (p=0.03).

Conclusions Plasmapheresis following IVMP therapy effectively removed anti-AQP4 antibodies and was accompanied by a substantial improvement in the neurological disability of patients with NMOSD. Lower levels of pre-existing neurological damage may be associated with an improved acute response to plasmapheresis. **J Clin Neurol 2013;9:36-42**

Key Words plasmapheresis, neuromyelitis optica, anti-aquaporin-4 antibody.

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Correspondence
Ho Jin Kim, MD, PhD
Department of Neurology,
Research Institute and
Hospital of National Cancer Center,
323 Ilsan-ro, Ilsandong-gu,
Goyang 410-769, Korea
Tel +82-31-920-2438
Fax +82-31-925-5524
E-mail hojinkim@ncc.re.kr

Introduction

Neuromyelitis optica (NMO) is an idiopathic inflammatory disease of the central nervous system (CNS) that is characterized by severe optic neuritis and myelitis. High-dose intravenous methylprednisolone (IVMP) is typically administered to treat acute exacerbations of NMO, but this is ineffective in some patients. Therapeutic plasmapheresis appears to be effective in patients with CNS inflammatory demyelinating diseases (IDDs) who do not recover after IVMP treatment. The efficacy of plasmapheresis may be due to the removal of circulating autoantibodies and other immunologically active substances (e.g., complement and cytokines) from the blood.[1] Since an autoantibody that targets aquaporin-4 (AQP4) was discovered in patients with NMO,[2] numerous clinical and experimental studies have implicated anti-AQP4 antibody-medi-

ated autoimmunity in the pathogenesis of NMO.[3-8] Accordingly, NMO may be particularly amenable to treatment by plasmapheresis. Previous studies and case series have found that plasmapheresis is effective in suppressing acute attacks in 50-89% of patients with NMO.[9-13] However, many of the previous observational studies on the clinical efficacy of plasmapheresis retrospectively evaluated all cases of CNS IDDs including NMO; thus, the exact efficacy of plasmapheresis for NMO attacks may have been underestimated.[9-11] Furthermore, recent plasmapheresis case series in patients with NMO involved small numbers of patients.[12,13] Plasmapheresis is becoming the preferred standard rescue therapy for NMO when high-dose IVMP treatment elicits only a weak response.[14-16] However, evidence for the therapeutic efficacy of plasmapheresis for acute attacks of NMO is still limited. Moreover, the extent to which anti-AQP4 antibodies are removed by plasmapheresis and whether removing anti-AQP4 antibodies is critical for the therapeutic efficacy of plasmapheresis in patients with NMO remain unclear.

The above situation prompted this study to assess the clinical efficacy and safety of plasmapheresis in patients with NMO spectrum disorder (NMOSD) and also to evaluate the changes in anti-AQP4 antibody levels following plasmapheresis.

Methods

Patients

We retrospectively reviewed the medical records of 15 patients who had NMO or who were seropositive for a limited form of NMO[17,18] and who had received plasmapheresis for acute attacks between March 2010 and September 2011. Plasmapheresis was performed when severe disability was sustained or worsened after high-dose IVMP therapy (1 g for 5 days) as indicated by Expanded Disability Status Scale (EDSS) scores ≥7.0 or a visual acuity worse than 20/200. Three patients had two series of plasmapheresis sessions with intervals of more than 6 months. Therefore, 18 plasmapheresis series performed in 15 individual patients were evaluated. This study was approved by the Institutional Review Board of the National Cancer Center (Protocol #NCCCTS-11-546), and informed consent was obtained from all patients.

Plasmapheresis

Patients were treated using double-filtration plasmapheresis (Plasauto EZ, Asahi Kasei Medical, Tokyo, Japan). Between 1 and 1.5 plasma volumes were treated in each session every other day. Vascular access was established with a double-lumen catheter in the central vein. All but one of the patients received tapered oral corticosteroids during plasmapheresis. Five patients were maintained on prior immunosuppressive treatments (mycophenolate mofetil or azathioprine) during the plasmapheresis. During double-filtration plasmapheresis, 5% albumin or normal saline was used as the replacement fluid. Each patient underwent six sessions of plasmapheresis.

Outcome assessments

Functional improvements immediately and 6 months after plasmapheresis were the primary outcomes, and changes in anti-AQP4 antibody levels following plasmapheresis were the secondary outcome measured. Because the EDSS focuses on ambulation-related disability, the targeted neurological deficit may not be fully reflected in the EDSS score (e.g., upper extremity paresis). Therefore, the outcome of plasmapheresis was evaluated according to the criteria of Keegan et al.[9] as follows: "no improvement" was defined as no improvement in neurological function, "mild improvement" presented as definite improvement in neurological status without impact on function, "moderate improvement" appeared as definite improvement in function (e.g., walking or the use of an upper extremity), and "marked improvement" was a major improvement in function. Either a "moderate improvement" or "marked improvement" was defined as a significant improvement. In parallel, the EDSS score was also evaluated in attacks that included myelitis or brain involvement, and visual acuity was assessed separately for each eye using the following Visual Outcome Scale (VOS): 0=20/20; 1=scotoma, but better than 20/30; 2=20/30-20/59; 3=20/60-20/199; 4=20/200-20/800; 5=able to count fingers only; 6=light perception; and 7=no light perception.[19] Adverse events were recorded throughout the study.

Blood collection and measurement of serum anti-AQP4 antibodies and cytokines

Serum samples were obtained before and after plasmapheresis for all attacks. Serum samples were also obtained pre- and poststeroid therapy and serially after each session in eight attacks. All samples were immediately centrifuged, and sera were stored at -80°C until analysis. The quantitative change in anti-AQP4 antibody levels was measured using an enzyme-linked immunosorbent assay.[20] The levels of anti-AQP4 antibody were quantified using a standard curve.

Statistical methods

Wilcoxon's signed-rank test for paired data was used to analyze the changes in the EDSS and VOS scores and the anti-AQP4 antibody level after plasmapheresis. Clinical variables were compared between patients with and without significant responses using the χ^2 for frequency comparisons and the Mann-Whitney test for mean comparisons. All statistical analyses were performed using GraphPad PRISM (San Diego, CA, USA), and probability values of $p<0.05$ were considered statis-

tically significant.

Results

Eighteen plasmapheresis treatments performed for acute attacks of NMOSD were evaluated in 15 patients (8 with NMO and 7 with a limited form of NMO). Thirteen patients (87%) were women. The median age at the time of plasmapheresis was 40 years (range, 12-53 years), and the median disease duration was 4 years (range, 0.1-13 years). Plasmapheresis was administered because of 11 optic neuritis attacks in 8 patients, 5 myelitis attacks in 5 patients, and 2 attacks involving the brain in 2 patients. Patients had a median of 5 relapses (range, 1-12) prior to treating an attack with plasmapheresis. The baseline VOS score for patients who had optic neuritis attacks was 1.1±1.2 (mean±SD), and the baseline EDSS score for patients who had attacks of myelitis or brain involvement was 3.5±2.5 (mean±SD). The immunotherapies that each patient received before plasmapheresis are listed in Table 1 and 2.

Plasmapheresis was associated with significant improvements immediately in 9 attacks (50%; 2 with moderate improvement and 7 with marked improvement) and with significant improvements at 6 months in 14 attacks (78%; 5 with moderate improvement and 9 with marked improvement). Neurological disability at relapse was severe (EDSS scores of 7.4±1.0 in patients with attacks of myelitis or brain involvement and VOS scores of 4.9±1.6 in patients with attacks of optic neuritis), but was sustained or worsened despite high-dose IVMP therapy (EDSS score, 7.6±0.7; VOS score, 4.8±0.9; p=0.180 and 0.527, respectively). Plasmapheresis was initiated at 16±8 days after the onset of symptoms. The neurological disability improved significantly upon the completion of plasmapheresis (EDSS score, 6.1±1.6; VOS score, 3.6±1.5; p=0.041 and 0.024, respectively) and further improved at 6 months following plasmapheresis (EDSS score, 4.6±1.8; VOS score, 2.6±1.6; p=0.016 and 0.009, respectively). Of the nine attacks showing

Table 1. Clinical characteristics, treatments, and outcomes of 11 optic neuritis attacks in 8 patients

Attack no./sex /age at plasmapheresis, years	Days from symptom onset to plasmapheresis	Type of lesion	VOS score before attack	VOS score at attack	VOS score after IVMP	VOS score upon completing plasmapheresis	VOS score at 6 months after plasmapheresis	Immuno-therapy before plasmapheresis
1/F/53	24	O	0	5.0	6.0	2.0	2.0	
2/F/49	18	O	0	1.0	4.0	2.0	0	
3/F/24	15	O	3.0	6.0	5.0	5.0	5.0	RTX
4/F/12‡	14	O	0	7.0	6.0	5.0	3.0	
5/F/37§	20	O	1.0	6.0	5.0	3.0	2.0	MMF
6/M/36	10	O*	0.0/2.0	3.0/4.0	3.0/4.0	3.0/4.0	3.0/4.0	
7/F/48†	11	O	0	5.0	4.0	2.0	1.0	
8/F/38§	12	O	2.0	4.0	4.0	4.0	3.0	RTX
9/F/12‡	16	O	3.0	6.0	6.0	6.0	4.0	MMF
10/F/35	10	O	0	5.0	4.0	2.0	1.0	MMF
11/F/48†	9	O	1.0	5.0	5.0	5.0	4.0	MMF

*Bilateral optic neuritis, †,‡,§Each patient had two separate attacks that were treated with plasmapheresis.
F: female, IVMP: intravenous methylprednisolone, M: male, MMF: mycophenolate mofetil, O: optic nerve, RTX: rituximab, VOS: Visual Outcome Scale.

Table 2. Clinical characteristics, treatments, and outcomes of 7 attacks involving the spinal cord or brain in 7 patients

Attack no./sex /age at plasmapheresis, years	Days from symptom onset to plasmapheresis	Type of lesion	EDSS score before attack	EDSS score at attack	EDSS score after IVMP	EDSS score upon completing plasmapheresis	EDSS score at 6 months after plasmapheresis	Immuno-therapy before plasmapheresis
1/F/51	18	B	0	8.5	8.5	5.5	3.0	
2/F/46	16	S	4.0	7.0	7.0	5.0	3.5	
3/F/30	45	S	4.5	6.5	7.0	6.5	5.0	
4/F/53	12	S	4.0	6.0	7.5	5.5	4.5	RTX
5/M/51	14	S	6.0	8.0	8.0	8.0	7.0	AZT
6/F/25	13	B	0.0	7.0	7.0	4.0	2.5	
7/F/43	9	S	6.0	8.5	8.5	8.5	7.0	

AZT: azathioprine, B: brain, RTX: rituximab, EDSS: Expanded Disability Status Scale, IVMP: intravenous methylprednisolone, S: spinal cord.

significant improvement upon the completion of plasmapheresis, the clinical response typically commenced after the third session (median value; range, sessions 1-4). Meanwhile, 5 of the 18 attacks (28%) showed no functional improvement upon the completion of plasmapheresis, but there was an improvement 6 months after plasmapheresis.

All patients were seropositive for anti-AQP4 antibodies. Plasmapheresis consistently resulted in a marked reduction in serum anti-AQP4 antibody levels (by 84.5±14.8% of the pre-plasmapheresis serum levels). We also investigated serial changes in anti-AQP4 antibody levels before and after steroid therapy and following every session of plasmapheresis in eight attacks (Fig. 1). The anti-AQP4 antibody levels decreased slightly after steroid therapy (by 14.3±15.2% of the pre-steroid-therapy level), but the decrease was significantly larger after plasmapheresis following all attacks. The reduction rate in anti-AQP4 antibodies of each sessions plateaued after the five sessions.

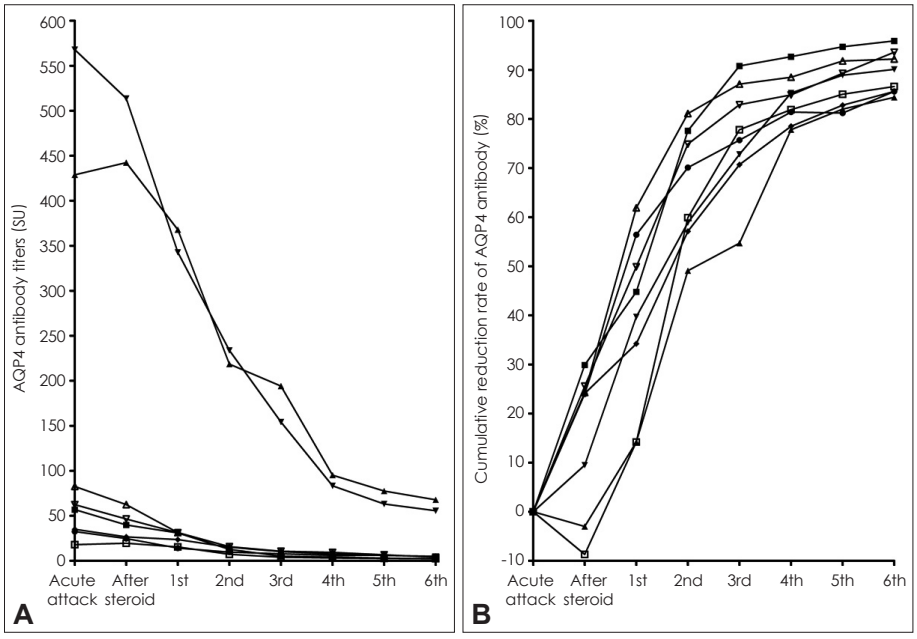

Fig. 1. Longitudinal titer (A) and cumulative reduction rate (B) of anti-aquaporin-4 (AQP4) antibodies before and after steroid therapy at each plasmapheresis session.

Table 3. Comparison of attacks with and without significant improvement upon the completion of plasmapheresis

Factor	Attacks with significant improvement (*n*=9)	Attacks without significant improvement (*n*=9)	*p*
Age at plasmapheresis, years	44.2±9.6	32.6±14.4	0.066
Females, *n* (%)	9 (100)	7 (78)	0.471
Disease duration, years (mean±SD)	5.2±4.9	4.7±3.6	1.000
Total number of attacks (mean±SD)	5.7±3.2	5.0±3.5	0.644
EDSS score before attacks of myelitis or brain involvement (mean±SD)	2.0±2.3	5.6±0.9	0.057
VOS score before attacks of optic neuritis (mean±SD)	0.2±0.4	1.8±1.2	0.030*
Interval to plasmapheresis, days	15.8±4.7	16.0±11.2	0.297
EDSS score at plasmapheresis onset in attacks of myelitis or brain involvement (mean±SD)	7.5±0.7	7.8±0.8	0.629
VOS score at plasmapheresis onset in attacks of optic neuritis (mean±SD)	4.6±0.9	5.0±0.9	0.537
EDSS score upon completion of plasmapheresis in attacks of myelitis or brain involvement (mean±SD)	5.0±0.7	7.7±1.0	0.032*
VOS score upon completion of plasmapheresis in attacks of optic neuritis (mean±SD)	2.2±0.4	4.8±0.8	0.004*
Immunosuppressive treatment before plasmapheresis, *n* (%)	3 (33)	5 (56)	0.637
Reduction rate in anti-AQP4 antibodies (%)	86.5	82.7	0.336

*Level of significance <0.05.
AQP4: aquaporin-4, EDSS: Expanded Disability Status Scale, VOS: Visual Outcome Scale.

No significant differences in sex ratio, age at the time of plasmapheresis, previous numbers of attacks, disease duration, attack severity, EDSS score before an attack, delay in plasmapheresis after symptom onset, or rate of reduction in anti-AQP4 antibodies were identified as an explanation for the variable acute response after the completion of plasmapheresis. However, lower VOS scores before an attack were associated with a significant immediate improvement upon the completion of plasmapheresis (p=0.03) (Table 3).

One patient developed anemia and one experienced hypokalemia, but no serious complications occurred during plasmapheresis. Significant transient leukocytosis (12000-22000/μL) was common immediately after plasmapheresis, but in all cases this reversed 1 day later. No clinical symptoms associated with transient leukocytosis were observed. Direct contact of blood mononuclear cells with the filter membrane may induce leukocytosis.[21]

Discussion

We analyzed the clinical effectiveness of therapeutic plasmapheresis and its effect on anti-AQP4 antibody levels in patients with acute attacks of NMOSD who responded insufficiently to high-dose IVMP therapy. Plasmapheresis following IVMP therapy was well tolerated. A significant functional improvement was seen in 50% of attacks immediately after the completion of plasmapheresis, and in 78% of attacks at 6 months after plasmapheresis. The response rate to plasmapheresis in our series is comparable to the response rates of 50-89% observed in NMO patients in previous studies.[9-13] Plasmapheresis was effective at decreasing anti-AQP4 antibody levels to 15% of the preplasmapheresis serum levels.

Considering the absence of controls, the observed effects in our study may be at least partly attributable to the natural course following attacks or to a delayed effect of IVMP therapy. However, immediate functional improvement following plasmapheresis was observed in half of the attacks that had been unresponsive to IVMP therapy or where the condition worsened despite the therapy. These results are consistent with a previous study finding significantly better outcomes in the steroid-and-plasmapheresis-treated group than in the steroid-only-treated group.[22] The clear temporal association between plasmapheresis and the clinical response over a short period of time in the present study suggests that this therapy is pivotal in facilitating recovery from neuronal injury. Although previous plasmapheresis studies involving CNS IDDs (including NMO) found rapid improvement in 33-37% of patients,[9,10] the heterogeneity of CNS IDD pathology may have influenced the response rate. Moreover, recent studies on CNS IDDs have concentrated on long-term efficacy, with the primary outcome being improvement at 6 months after plasmapheresis.[11] Thus, the beneficial effects of the acute response may have been underestimated.[11] Considering humoral immunity-mediated immunopathogenesis in NMO, the acute response following plasmapheresis may be more profound than that in other CNS IDDs. Indeed, the observation of the rate of acute improvement being higher (50%) in this study than in previous studies including all CNS IDDs[9,10] may indicate that the acute therapeutic efficacy of plasmapheresis in NMOSD is better than previously thought. Similarly, a recent case series found rapid clinical improvement following plasmapheresis in 50-67% of patients with NMO.[12,13]

The immediate response to plasmapheresis in acute attacks of NMO may be related to a rapid reduction in anti-AQP4 antibody levels. The anti-AQP4 antibody levels declined by an average of 14% of the initial levels following IVMP therapy (with little variation), whereas an average of six sessions of plasmapheresis consistently induced marked reductions (85%) relative to the preplasmapheresis levels (Fig. 1). This observation agrees with previous findings that the exchange molecules decreased to less than 20% of their initial level after five sessions.[23,24] The rate of reduction of anti-AQP4 antibodies was greatest at the beginning of plasmapheresis and reached a plateau after five sessions (Fig. 1). Therefore, at least five sessions of plasmapheresis might be required to effectively remove anti-AQP4 antibodies. Similarly, previous studies have suggested that five or six standard plasmapheresis sessions are required to substantially reduce blood levels of IgG.[25] However, the optimal minimum number of sessions for clinical recovery still needs to be determined.

Meanwhile, the reduction rate of anti-AQP4 antibodies did not differ significantly between attacks with and without significant improvement upon the completion of plasmapheresis. This finding suggests that a reduction in anti-AQP4 antibody is not the only factor affecting the clinical efficacy of plasmapheresis. In the present study, a significant improvement upon the completion of plasmapheresis was associated with a low baseline level of neurological disability. The baseline VOS score was much higher in attacks that showed no significant improvement than in those with significant improvement (p= 0.03) (Table 3). This observation indicates that the extent of pre-existing neuronal damage and the "neurologic reserve" to promote restoration may be important factors for clinical recovery following plasmapheresis. This hypothesis was supported by the clinical results seen in three patients in whom two series of plasmapheresis were applied on the same lesion for two separate attacks. All three patients achieved significant improvements following the first plasmapheresis series; however, the clinical response was much slower after the second plasmapheresis series than after the first series in all three pa-

tients, and one patient showed no functional improvement following the second series. Bonnan and colleagues suggested that a low basal impairment is associated with a better outcome.[22] A recent study also found that a shorter disease duration was associated with a beneficial response to plasmapheresis, which is roughly consistent with our findings.[11] Additionally, previous studies involving patients with CNS IDDs found that starting plasmapheresis early (within 15 to 20 days) is the most important predictor of a favorable response to the procedure.[9-11] However, plasmapheresis was initiated within 20 days in 89% of our patients, which might explain why the time interval to plasmapheresis appeared to have no significant association with clinical efficacy upon the completion of plasmapheresis in the present study.

Plasmapheresis did not initially result in significant improvement for five attacks (28%), although there was a marked improvement at 6 months after plasmapheresis. This result agrees with previous observations of delayed responses in 4-48% of patients.[9-11] Actually, most of the attacks in our series were further improved at 6 months after plasmapheresis. Whether the late improvement is a delayed effect of plasmapheresis or the natural course of the disease remains uncertain. Nevertheless, the effective removal of anti-AQP4 antibodies by plasmapheresis may be beneficial in preventing further attacks for a period of time and thus providing patients with an extended recovery time without further relapse, which may positively influence the clinical course of the disease.

Our analysis was limited by the study having a retrospective design, being based in a single center, examining only a small number of patients, and not including a control group of patients with similar symptoms who did not receive plasmapheresis. However, considering the rarity of the disease, the limited evidence for the efficacy of plasmapheresis in NMO, and the ethical difficulties in conducting randomized controlled trials, our data provide clinical and laboratory support for the value of plasmapheresis in steroid-resistant acute attacks of NMO.

In conclusion, plasmapheresis should be considered for NMOSD patients with severe attacks who do not respond to IVMP therapy. The extent of the underlying neuronal damage may influence the acute response to plasmapheresis. Further clinical trials are needed to confirm the reported findings and identify the optimal protocol for delivering plasmapheresis.

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