Therapeutic Apheresis and Dialysis

Therapeutic Apheresis and Dialysis 15(5):493–498
doi: 10.1111/j.1744-9987.2011.00960.x

Role of Plasmapheresis Performed in Hemodialysis Units for the Treatment of Anti-Neutrophilic Cytoplasmic Antibody-Associated Systemic Vasculitides

Zeki Aydin, Meltem Gursu, Serhat Karadag, Sami Uzun, Emel Tatli, Abdullah Sumnu, Savas Ozturk, and Rumeyza Kazancioglu

Department of Nephrology, Haseki Training and Research Hospital, Istanbul, Turkey

Abstract: Anti-neutrophilic cytoplasmic antibody (ANCA) positivity is seen in some systemic necrotizing vasculitides. Wegener's granulomatosis and microscopic polyangiitis are among the ANCA-associated systemic vasculitides (AASV) and mortality is very high when renal failure occurs together with alveolar hemorrhage. The role of plasmapheresis in the treatment of these diseases has been studied retrospectively. Twelve patients with AASV who had plasmapheresis together with immunosuppressive medications have been involved. Primary diseases, immunosuppressive protocols, the number of plasmapheresis sessions, the amount of plasma that has been exchanged, urea and creatinine levels before and after treatment, pulmonary findings, the need for hemodialysis, and the outcome of patients were recorded. The mean age of patients was 52.9 ± 18.2 years. Wegener's granulomatosis was diagnosed in seven (58.3%) and microscopic polyangiitis in five (41.7%) patients. All patients had pulse cyclophosphamide and methylprednisolone followed by maintenance doses and plasmapheresis. Seven patients had hemodialysis at the beginning, and hemodialysis needed to be continued in three patients. Partial and complete remission was seen in 6 (50%) and 3 (25%) patients, respectively, and pulmonary findings regressed in all patients. End-stage renal disease develops generally in AASV due to rapidly progressive glomerulonephritis causing severe irreversible glomerular damage. The mortality rate rises to 50% in cases of renal failure with diffuse alveolar hemorrhage; therefore, pulse immunosuppressive treatment with plasmapheresis may be life-saving, as shown in our study. **Key Words:** Anti-neutrophilic cytoplasmic antibody, Microscopic polyangiitis, Vasculitis, Wegener's granulomatosis.

Anti-neutrophilic cytoplasmic antibody (ANCA) positivity is seen together with some systemic necrotizing vasculitides, of which Wegener's granulomatosis (WG) and microscopic polyangiitis (MPA) are the most important. Wegener's granulomatosis is a rare, multi-systemic disease that is characterized by necrotizing granulomatous vasculitis of the upper and lower respiratory tracts, kidneys, and some other organs (1). It may be an indolent disease without obvious clinical findings or may result in death within weeks. The presence of serious alveolar hemorrhage and/or renal failure increases the mortality rate of the disease markedly (1).

Received October 2010; revised March 2011.
Address correspondence and reprint requests to Dr Zeki Aydin, Haseki Eğitim ve Araştırma Hastanesi, Nefroloji Kliniği, Adıvar Caddesi, Aksanay, Istanbul 34090, Turkey. Email: zekiaydindr@yahoo.com

Microscopic polyangiitis is a multi-systemic, necrotizing, non-granulomatous vasculitis of the small vessels (capillaries, venules, and arterioles) with minimal or no immune deposition (2). It frequently involves lungs, kidneys and the skin; and is characterized by ANCA positivity, crescentic glomerulonephritis, pulmonary capillaritis, and the absence of immune deposits in biopsy specimens (3). It has a mildly higher prevalence in males and the age of onset is usually fifty years (2).

The annual incidence of ANCA-associated systemic vasculitides (AASV) is about 20 per million population and they frequently lead to end-stage renal disease (ESRD). They are the most frequent causes of rapidly progressive glomerulonephritis (RPGN) leading to ESRD in spite of immunosuppressive treatment. Mortality is very high in the case of alveolar hemorrhage together with acute renal

failure; wherein therapeutic plasma exchange (TPE; plasmapheresis) may be life saving (4–7).

Therapeutic plasma exchange is a form of extracorporeal circulation to extract high molecular weight substances from the plasma (6,7). Although this can be carried out by membrane separation and centrifugation techniques, the first method is more commonly used due to the need for less equipment and convenience for application in hemodialysis units. We retrospectively analyzed the role of plasmapheresis practiced in our hemodialysis unit in the treatment of AISV in conjunction with immunosuppressive therapies.

PATIENTS AND METHODS

Twelve patients (six male and six female) who were treated with plasmapheresis plus immunosuppressive medications for a diagnosis of AASV between October 2008 and July 2010 were involved in the study. The demographic data (age, gender, weight), primary diseases, the type and titer of ANCA, immunosuppressive treatment protocols, details about plasmapheresis (number of sessions and amount of plasma exchanged), urinary findings, findings of pulmonary involvement, the need for hemodialysis and the outcome of the primary disease were recorded for all patients. Regarding the laboratory analysis, urea and creatinine levels, creatinine clearance as calculated by the Cockcroft–Gault formula before and after treatment, erythrocyte sedimentation rate (ESR), ferritin, C-reactive protein (CRP), and hematocrit levels were recorded.

The clinical, laboratory and radiological findings of the patients were graded using the Birmingham Vasculitis Activity Score (BVAS) version 3 (8–10). The state of remission was evaluated at the end of the fourth month of treatment. Complete remission was defined as full recovery of the clinical findings and return of the laboratory values to normal limits with a BVAS value of zero. Patients were considered to be partial responders if hemodialysis was no longer needed and the creatinine level had decreased to levels below the initial value, together with the disappearance of extra renal findings, and thus a decrease in BVAS.

ANCA was examined using the indirect immunofluorescence method and was classified as cytoplasmic (c-ANCA/PR3-ANCA) or perinuclear (p-ANCA/MPO-ANCA) according to the appearance.

All patients had pulse cyclophosphamide treatment given as six pulses (0.5 g/m^2) every other three weeks, combined with pulse methylprednisolone 1 g/day for the first three days, followed by oral methylprednisolone at a dose of 1 mg/kg/day for one month, then tapered and discontinued within the next four months. Plasmapheresis was started concomitantly with immunosuppressive treatment, every day in the first week, then every other day until the clinical findings, especially alveolar hemorrhage, resolved.

The procedure was performed using a Prismaflex machine (Gambro, Lund, Sweden). The patient's plasma volume was calculated using the formula: plasma volume (L) = weight × 0.065 × (1 – hematocrit) (7). Fresh frozen plasma (FFP) was used as the replacement fluid.

The data were analyzed using SPSS for Windows, version 13.0 (SPSS, Cary, NC, USA). Numeric values were expressed as mean ± standard deviation. The paired Student's *t*-test and Mann Whitney U-test were used for intergroup comparisons. *P* values <0.05 were accepted as statistically significant.

RESULTS

The mean age of the patients was 52.9 ± 18.2 years. The diagnosis was WG in seven (58.3%) and MPA in five (41.7%) of the patients (Table 1). All patients received standard immunosuppressive treatment together with plasmapheresis. The mean follow-up period and the length of hospitalization were 9.8 ± 6.2 months and 34.9 ± 21.9 days, respectively. All of the patients had microscopic hematuria and proteinuria (2250 ± 1200 mg/day). Other laboratory parameters at the start of treatment were as follows: hematocrit 28.1 ± 4.5%, ESR 69.8 ± 41.1 mm/h, CRP 79.4 ± 116.4 mg/dL, and ferritin 684 ± 326 mg/L (Table 2). The mean amount of FFP used in 10.9 ± 3.5 (range, 4–14) sessions of plasmapheresis was 3080 ± 375 mL (2640–3960 mL) (Table 1). No complication was noted during the procedures.

Seven patients (58.3%) needed hemodialysis at the time of diagnosis, of which three (25%) remained hemodialysis dependent, while six (50%) had partial and three (25%) had complete remission (Table 2).

At the onset of treatment, microscopic hematuria was found in all patients, but had resolved with treatment in the complete responders. The level of proteinuria decreased from a mean of 3396 ± 1863 mg/day to levels less than 500 mg/day in patients having undergone complete remission. In those with partial remission, the average daily proteinuria was 2544 ± 1863 mg at the start of treatment, which decreased to 1005 ± 1090 mg with treatment.

TABLE 1. *Demographic data, clinical findings and data regarding plasmapheresis*

Patient	Age (years)	Gender	Weight (kg)	Diagnosis	Amount of FFP (mL)	Number of PP sessions	HD therapy, before treatment	HD therapy, after treatment	Alveolar hemorrhage	BVAS before and after treatment
1	57	Male	73	WG	3960	14	Yes	No	+	26/14
2	42	Female	50	WG	2860	14	Yes	Yes	+	21/12
3	63	Female	58	WG	2640	13	Yes	Yes	+	21/14
4	24	Male	62	WG	2860	7	No	No	+	27/0
5	57	Male	55	MPA	3080	4	Yes	No	–	20/8
6	32	Male	65	WG	3300	10	No	No	+	20/0
7	77	Female	72	MPA	2860	7	Yes	No	–	15/12
8	58	Male	57	MPA	3080	14	Yes	Yes	+	20/18
9	66	Female	50	MPA	2640	14	No	No	–	15/12
10	37	Male	67	WG	3080	14	No	No	+	17/0
11	39	Female	96	WG	3520	10	No	No	+	23/7
12	83	Female	62	MPA	3080	10	Yes	No	–	18/14

BVAS, Birmingham Vasculitis Activity Score; FFP, fresh frozen plasma; HD, hemodialysis; MPA, microscopic polyangiitis; PP, plasmapheresis; WG, Wegener's granulomatosis.

TABLE 2. *Laboratory findings and treatment outcomes of the patients*

Patient	ANCA type	ANCA titers before and after treatment (U/mL)	Hct (%)†	Creatinine before and after treatment (mg/dL)	Creatinine clearance before and after treatment (mL/min/1.73 m^2)	HD need before and after treatment	ESR before and after treatment (mm/h)	CRP before and after treatment (mg/dL)	Ferritin (mg/L)†	Treatment outcomes (remission)
1	cANCA	479/110	22.3	8.35/3.0	10.1/28	+/–	144/19	300/5	459	Partial
2	cANCA	300/None	22.6	9.5/9.5	6.1/6.1	+/+	125/49	197/7	660	No remission
3	cANCA	300/None	26.0	7.2/7.2	7.3/7.3	+/+	35/22	48.8/10	892	No remission
4	cANCA	300/26	38.0	2/1.4	50/66.6	–/–	88/36	300/2	727	Complete
5	pANCA	41.9/10	27.3	5.1/2.2	12.4/28.9	+/–	4/6	7.9/6	1400	Partial
6	cANCA	300/2.1	29.5	1.7/1.0	57.3/97.5	–/–	110/16	0.02/0.4	508	Complete
7	pANCA	40.2/10.8	29.0	4.5/3.0	11.9/17.8	+/–	66/12	55.7/7	482	Partial
8	pANCA	49.4/28	22.8	7.8/7.8	8.3/8.3	+/+	32/20	9.9/11	2000	No remission
9	pANCA	97.6/14	29.0	4.8/2.2	9.1/19.8	–/–	79/14	4.0/0.8	398	Partial
10	cANCA	300/1.2	32.2	0.9/1.0	106.5/95.7	–/–	56/12	11.2/0.1	392	Complete
11	cANCA	315/1.7	30.0	3.1/1.9	36.9/60.2	–/–	47/6	1.9/0.3	402	Partial
12	pANCA	274/3.2	28.7	5.8/1.9	7.2/22	+/–	52/30	15.7/1.7	593	Partial

†Values before treatment. ANCA, anti-neutrophilic cytoplasmic antibody; c, cytoplasmic; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; Hct, hematocrit; HD, hemodialysis; p, perinuclear.

The mean CRP levels and ESR of the patients overall were 79.4 ± 116.4 mg/dL and 69.8 ± 41.1 mm/h, respectively, at the onset, and 4.3 ± 3.9 mg/dL and 20 ± 13 mm/h at the end of the initial treatment. The mean cANCA and pANCA levels were 327 ± 67 U/mL and 101 ± 99 U/mL at onset, respectively, and the corresponding values were 28.2 ± 47 U/mL and 13.2 ± 9.2 U/mL at the end of the initial treatment, respectively (Table 2).

The mean creatinine levels before and after treatment were 5.06 ± 2.79 mg/dL and 3.39 ± 2.70 mg/dL, respectively ($P = 0.005$). Creatinine clearance was 26.9 ± 30.9 mL/min and 38.2 ± 33.3 mL/min before and after treatment, respectively ($P = 0.014$). When patients with WG and MPA were evaluated as different groups, the basal creatinine levels were significantly higher in those with MPA (4.68 ± 3.56 vs. 5.60 ± 1.32 mg/dL, $P = 0.003$), while they were similar after treatment (3.49 ± 3.21 vs. 3.26 ± 2.13 mg/dL, $P = 0.242$). The pulmonary findings, which were present in all patients except four with MPA, resolved after treatment.

At the time of diagnosis, the BVAS of the patients was 20.2 ± 3.8, decreasing to 8.4 ± 6.2 with treatment. The score was 21.3 ± 5.1 before and 0 after treatment in patients with complete remission, while the corresponding values were 19.5 ± 4.4 and 9.5 ± 3.8 in those with partial remission. Patients without remission had a BVAS of 20.7 ± 3.8, which decreased to 14.7 ± 3.0 after treatment (Table 1).

DISCUSSION

The combination of plasmapheresis with immunosuppressive medication adds much to the recovery of renal function in cases with serious acute renal failure. Plasmapheresis should be considered for all patients with severe alveolar hemorrhage, those with increasing hemoptysis despite conventional immunosuppressive treatment, and those with advanced renal failure (creatinine >5.7 mg/dL and/or the need for hemodialysis) (4). It has been reported in studies involving patients with RPGN, whether or not they have ANCA-associated vasculitis, that immunosuppressive treatment does not have an advantage regarding serum creatinine levels (11,12) and patient survival (12). But studies involving patients with ANCA-associated systemic vasculitis have shown that plasmapheresis therapy has positive effects on renal and patient survival (4–7,13). Anti-glomerular basement membrane (anti-GBM)-antibody mediated disease is another indication for plasmapheresis. Our patients, who were all negative for anti-GBM antibodies, received plasmapheresis due to clinical findings. The recommended dose is seven sessions within two weeks (4). FFP should be preferred in place of albumin in these cases to add to the coagulation cascade, as these patients have either alveolar hemorrhage or have undergone renal biopsy (4). In the present study, FFP (3080 ± 375 mL in each session) was used as the replacement fluid.

Patients with alveolar hemorrhage are advised to be treated with plasmapheresis, although there have been no randomized controlled trials (5,6). The mentioned treatment is effective especially in those with positive anti-GBM antibodies together with ANCA positivity. In an uncontrolled retrospective study of 20 patients with diffuse alveolar hemorrhage and ANCA-associated vasculitis, 14 had renal failure (creatinine ≥4.7 mg/dL) (6). All had daily plasmapheresis until the recovery of alveolar hemorrhage, followed by plasmapheresis every other day, and combined with 7 mg/kg/day methylprednisolone for the first three days and cyclophosphamide 0.5 g/m^2/day for the first two days. Among the 20 patients, nine needed ventilatory support, while seven had hemodialysis therapy. Alveolar hemorrhage recovered in all and none of them required ongoing hemodialysis. There were no serious complications recorded during the mean 6.15 (range, 4–9) sessions of plasmapheresis; however, one patient died due to pulmonary embolism. Similarly, the mean creatinine level before treatment was 5.06 ± 2.79 mg/dL in our study. Seven patients required hemodialysis therapy, with three of them still on a chronic hemodialysis program despite immunosuppressive treatment combined with plasmapheresis. Only one had a renal biopsy that showed diffuse fibrous crescents. No complications were recorded during the sessions, the mean number of which was 10.9 ± 3.5 sessions. One patient with a partial response died due to acute respiratory distress syndrome.

In a randomized controlled trial in which plasmapheresis was compared with pulse methylprednisolone in patients with severe renal failure, 137 patients with WG, MPA or pauci-immune glomerulonephritis were enrolled (4). The mean creatinine level was 8.3 mg/dL (all above 5.7 mg/dL) and 69% of the patients needed hemodialysis. Patients were randomized to be treated with either seven sessions of plasmapheresis within two weeks or methylprednisolone 1 g/day for three days, followed by therapy with prednisolone 1 mg/day for six months and cyclophosphamide 2.5 mg/day for three months. This remission protocol was followed by maintenance treatment with azathioprine. It was shown that patients treated with plasmapheresis had better preserved renal function and less probability of developing ESRD (19 vs.

43%), although there was no statistically significant difference between the one-year survival rates. The reasons for death, most of which occurred in the first three months, were infections in 19, pulmonary hemorrhage in six, and cardiovascular events in four patients. This study showed that treatment outcomes are better when immunosuppressive therapies are combined with plasmapheresis in patients with creatinine levels above 5.7 mg/dL (4). In our study, a total of 10.9 ± 3.5 sessions of plasmapheresis were combined with pulse methylprednisolone and cyclophosphamide therapy. Prednisolone 1 mg/kg/day and cyclophosphamide 0.5 g/day/m^2 every three weeks were used as maintenance treatment. Pretreatment creatinine levels decreased from 5.06 ± 2.79 mg/dL to 3.39 ± 2.70 mg/dL ($P = 0.005$), pretreatment creatinine clearances increased from 26.9 ± 30.9 mL/min to 38.2 ± 33.3 mL/min ($P = 0.014$), and the number of patients requiring hemodialysis decreased from seven to three patients. Clinical and radiological pulmonary findings of the eight (66.7%) patients who had alveolar hemorrhage at the start resolved completely.

In a national survey published by Yamagata et al. (14) with patients having RPGN due to MPO-ANCA associated vasculitis, it was demonstrated that patients with PR3-ANCA positivity ($N = 23$) have a more rapidly progressive course than those without PR3-ANCA positivity ($N = 370$). It was also shown that MPO-ANCA titers dropped with plasmapheresis more rapidly and the patient survival was better (66.7 vs. 56.7%). Plasmapheresis has been reported as a good treatment option for ANCA-associated RPGN and renal pulmonary syndromes. In our study, all patients with positive PR3-ANCA had alveolar hemorrhage and higher levels of CRP (123 ± 139 vs. 18 ± 21 mg/dL) and ESR (86 ± 42 vs. 47 ± 29 mm/h), and lower creatinine (4.68 ± 3.56 vs. 5.6 ± 1.32 mg/dL) levels. The rate of decrease in creatinine levels in MPO-ANCA positive and PR3-ANCA positive patients were 41.8% and 25.4%, respectively. The response to treatment was more pronounced in those with MPO-ANCA positivity.

Another important finding of our study was that the BVAS of patients with complete remission decreased dramatically when compared with the total population of our patients (21.3 ± 5.1 and zero vs. 20.2 ± 3.8 and 8.4 ± 6.2). In our study it was shown that ANCA titers dropped rapidly with plasmapheresis treatment, but there was no significant correlation between the state of remission and ANCA titers. All the patients who had complete remission were those with WG. This may be related to the indication for plasmapheresis being alveolar hemorrhage rather than obvious elevations in creatinine levels.

CONCLUSION

Plasmapheresis was used in our patients due to the presence of severe uremia and/or active alveolar hemorrhage, which are urgent cases. There are no randomized controlled trials in the literature comparing plasmapheresis with other treatment modalities. Although the number of patients is limited, our study shows that plasmapheresis adds to treatment success. Patients with diffuse alveolar hemorrhage together with acute renal failure should be started on immunosuppressive therapy together with plasmapheresis as soon as possible due to high mortality rates (up to 50%).

Another aspect of our study is that all sessions were performed in our hemodialysis unit. Plasma exchange with a centrifugation technique is an expensive treatment modality that requires specialist equipment not available in most care facilities. Keeping in mind the urgency of treatment, it is very advantageous to be able to perform plasma exchange with the membrane separation technique without the need for equipment further than what is present in most hemodialysis units. Finally, hemodialysis staff, especially nephrologists, should be involved in the treatment of AASV with plasmapheresis.

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