J Tokyo Wom Med Univ
79 (1) 9～17 (2009)

Original

Short-Term Effects of Apheresis on Renal Function and Proteinuria in the Treatment of Rapidly Progressive Glomerulonephritis

Masae AKAO[1], Keiko UCHIDA[1], Kan KIKUCHI[2], Wako YUMURA[3] and Kosaku NITTA[1]

[1]Department of Medicine IV (Director: Prof. Kosaku NITTA), Tokyo Women's Medical University, School of Medicine
[2]Department of Blood Purification, Kidney Center, Tokyo Women's Medical University
[3]Department of Nephrology, Jichi Medical University

(Accepted Nov. 4, 2008)

For rapidly progressive glomerulonephritis (RPGN), immunosupressants such as steroids constitute a major therapy, and apheresis is done on a case by case basis. The aim of the present study to assess the efficacy of apheresis in the treatment of RPGN. We investigated the clinical course of 39 patients with RPGN during the 10 years from 1995 to 2005, retrospectively. They were divided into two groups, apheresis group and non-apheresis group. All patients except one were administrated steroids. Nine patients in apheresis group were carried out double filtration plasmapheresis or single plasma exchange and there were 2-7 sessions per case. There were no statistically significant differences in the renal function as estimated by serum creatinine levels or inflammatory reactions. The average amounts of proteinuria were 3.4±2.5 g/day (0.38-6.44 g/day) in the apheresis group and 1.5±1.4 g/day (0.12-5.58 g/day) in the non-apheresis group (p=0.007). However, total steroid dosages were 0.49± 0.22 mg/kg/day in the apheresis group and 0.63±0.16 mg/kg/pay in non-apheresis group, indicating a significantly smaller steroid dose in the apheresis group (p=0.04). Finally, we found better renal prognosis and mortality in the apheresis group. These results suggest that apheresis has an advantage in the treatment of RPGN patients in terms of the improvements of renal and life prognosis.

Key words: rapidly progressive glomerulonephritis, plasmapheresis, ANCA, vasculitis, proteinuria

Introduction

Rapidly progressive gromerulonephritis (RPGN) is defined by the World Health Organization (WHO) as a hematuria crisis of sudden or insidious onset, proteinuria, anemia and progressive renal insufficiency. Generally speaking, from a histological perspective, nephritides forming necrotizing crescents, cellular crescent formation of multiple glomeruli are common[1]. RPGN is a clinical syndrome, and according to the classification by Couser et al[2], the basal disease is classified into 3 types, i.e. Type I of glomerular basement membrane antibody type, Type II of RPGN immunocomplex type, and Type III of RPGN pauchi-immune type.

In Japan, according to research on progressive renal insufficiency by the Ministry of Health, Labour and Welfare published in 1999, the pauci-immune type shows frequent serum antineautrophil cytoplasm autoantibodies (ANCA)-positivity (39.6%), anti- glomerular basement membrane (GBM) antibody type (6.5%), immunocomplex type (3.4%), microscopic polyangitis (17.8%), Wegener's granulomatosis (2.5%), and systemic lupus erythematosus (5.9%) respectively. However RPGN in the US and Europe has higher rates of anti-GBM vasculitis somewhat different from ours[3].

For this disease, immunosuppressants such as steroids constitute a major therapy, and apheresis is done on a cases by case basis. In Europe, apheresis is recommended for cases with anti-GBM antibodies, ANCA positive cases with high serum creatinine (Cr) levels, and cases with pulmonary hem-

orrhages. In Japan, RPGN therapy guidelines have not included apheresis. However, as some randomized controlled trials (RCT) and case series reported the usefulness of apheresis, we have conducted investigations retrospectively for 10 years and studied renal and life prognoses in our hospital.

Patients and Methods

1. Patients

Sixty-four patients, who were diagnosed with RPGN clinically based on the WHO definition, among all patients hospitalized in the Division of Nephrology during the 10 years from 1995 to 2005, were study subjects. Renal biopsy was performed in 36 cases of RPGN patients. Those with therapies started from the time of admission, RPGN recrudescence, collagenosis, drug-induced RPGN, and subjects not showing crescent formation, despite renal biopsy, were excluded.

2. Treatment regimen

All 39 patients, who became subjects, were on steroids except one who was included in the apheresis group. Some received steroids pulse therapy, while others did not. In each group the rate of patients who received steroid pulse therapy against those who did not receive it did not show statistical difference (6/9 patients of the former group received steroid pulse therapy, while 17/30 patients of the latter received it; p=0.59). As for steroids, both prednisolone and methyl-prednisolone were used. Converted into methyl-prednisolone, a total dosage for 8 weeks was calculated, and the average daily dose per 1 kg of patient weight was studied. Two types of apheresis were conducted double membrane filtration and single plasma exchange. For the double membrane filtration on a plasma separator, the plasma flow was achieved with an Asahi Medical Co., Limited device and an Evaflux 2A (Kuraray Medical Corp) was used secondarily. The fluid substitution in one session of double membrane filtration was 8% albumin 500 ml (a blood cleaner KPS 8800CE or KM 8800), and plasma flow was used for simple plasma exchanges to achieve exchanges of 46.5±5.4 ml/kg with fresh frozen plasma. There were 2-7 sessions, or 3.4±1.4 times sessions on average, per case.

3. Patient follow up

At the time of admission, serum Cr, serum total protein and albumin, urea nitrogen, CRP, proteinuria level, uro-hematid numbers, 24 hours creatinine clearance as the glomerular filtration rate, and serum ANCA antibody titer (ELISA Method, Biocarb Diagnostics, Sweden) were evaluated. As for serum Cr, proteinuria and serum ANCA titers, the amounts measured 8 weeks after starting therapy were compared. In addition, to judge the initial therapy efficacy, renal and life prognoses were studied.

4. Statistical analysis

For the statistical analysis, each index was expressed using the average±standard deviation. Student's t-tests were used to determine the significance of differences between two groups. The rate of patients with or without steroid pulse therapy was analyzed using the χ^2 test. In order to examine if apheresis is independent indicator to predict the renal outcome, multivariate analyses were performed using JMP version 5.1 (SAS for Windows, Cary, NC, USA) as the software. The dependent variable were serum Cr values and independent variables were age, sex, proteinuria, MPO-ANCA titer, Cr, CRP, total steroid doses and apheresis. Because renal biopsy was not performed in all patients, pathological findings were not included in the independent variables. P value <0.05 was considered significant for every test.

Results

The ages of the 64 RPGN patients were 16-81, males 39, and females 25. The 24 excluded cases were 6 RPGN with recurrences, 8 who already had a therapy history on admission, 2 drug induced disease, and 2 with acute glomerulonephritis. There was one case each of end-stage renal failure, diabetes mellitus, focal segmental gomerulosclerosis, membranous nephropathy, hypohydremia, mixed connective disease and tubular disease. The 39 RPGN patients were 28-79 years of age (average 62.3±12.9), males 17 and females 22. Renal biopsy was conducted on 27/39 (62.5%). Apheresis was carried out in 9 of the 39, including 5 double filtration plasmapheresis cases and 4 simple plasma ex-

Table 1 The original disease in patients with RPGN studied

	Apheresis group (9)	Non-apheresis group (30)
MPO-ANCA associated vasculitis	3	18
MPO-ANCA associated nephritis	2	7
Pauci-immune glomerulonephritis without ANCA	1	0
Anti-GBM antibody nephritis	1	2
PR3-ANCA associated vasculitis	0	1
IgA nephropathy	2	2

RPGN: rapidly progressive glomerulonephritis, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody, GBM: glomerular basement membrane.

Table 2 Comparison of clinical parameters between apheresis group and non-apheresis group on admission

	Apheresis group	Non-apheresis group	
Number of patients	9	30	n.s.
Male/Female	6/3	11/19	n.s.
Age [year]	55.9 ± 12.7	64.2 ± 12.5	n.s.
RBC [/high-power field]	77.2 ± 31.5	54.4 ± 38.6	n.s.
proteinuria [g/day]	3.4 ± 2.5	1.5 ± 1.4	p = 0.007
24hCcr [ml/min]	21.5 ± 17.1	19.3 ± 18.6	n.s.
Serum total protein [g/dl]	6.3 ± 0.6	6.4 ± 0.7	n.s.
Serum albumin [g/dl]	3.1 ± 0.5	3.1 ± 0.9	n.s.
BUN [mg/dl]	51.3 ± 27.0	48.9 ± 30.0	n.s.
Serum creatinine [mg/dl]	4.7 ± 2.7	4.4 ± 3.0	n.s.
CRP [mg/dl]	4.9 ± 8.3	9.3 ± 9.9	n.s.
WBC [/μl]	9,714.4 ± 4,446.2	11,125.7 ± 5,206.1	n.s.
MPO-ANCA [IU/ml]	368.6 ± 315.9	388.8 ± 2,971.0	n.s.

RBC: red blood cells, Ccr: creatinine clearance, BUN: blood urea nitrogen, CRP: C-reactive protein, WBC: white blood cells, MPO-ANCA: myeloperoxidase-antineutrophil cytoplasmic antibody.

change cases.

The original disease in RPGN was shown in Table 1. MPO-ANCA associated disease was seen in 5/9 (55.6%) in the apheresis group and 25/30 (83.3%) in the non-apheresis group. It accounted for the majority in both groups. Anti-GBM antibody nephritis was seen in 1 apheresis group case and 2 non-apheresis group cases. The patient with anti-GBM antibody nephritis in the apheresis group also had pulmonary hemorrhage at the time of admission, her serum Cr was 9.39 mg/dl, and hemodialysis was needed during therapy. Another patient in the non-apheresis group had a serum Cr of 1.73 mg/dl. According to our RPGN criteria, each group included 2 IgA nephritis cases, while others had only vasculitis.

Table 2 shows the characteristics of each group on admission. No difference in age or sex was observed in the either group. On blood tests, the average serum Cr level was 4.7±2.7 mg/dl in the apheresis group and 4.4±3.0 mg/dl in the non-apheresis group. CRP was 4.9±8.3 mg/dl in the former, and 9.3±9.9 mg/dl in the latter, and there were no statistically significant differences in renal function or inflammatory reactions. As for proteinuria, on admission 4/9 were in a nephritic state in the former, 4/30 in the latter, and the average amount was 3.4±2.5 g/day (0.38-6.44 g/day), with only the 1.5±1.4 g/day (0.12-5.58 g/day) difference being significant ($p=0.007$). Concerning MPO-ANCA positive patients, the titer was 368.6 ± 315.9 IU/ml in the former, 388.8±297.0 IU/ml in the latter, and the difference was not significant. In treatment regimen, cyclophosphamide therapy was added to 2 patients in apheresis group and 1 patient in non-aphersis group.

Fig. 1 shows proteinuria reduction rate 8 weeks after starting treatments. As compared with the

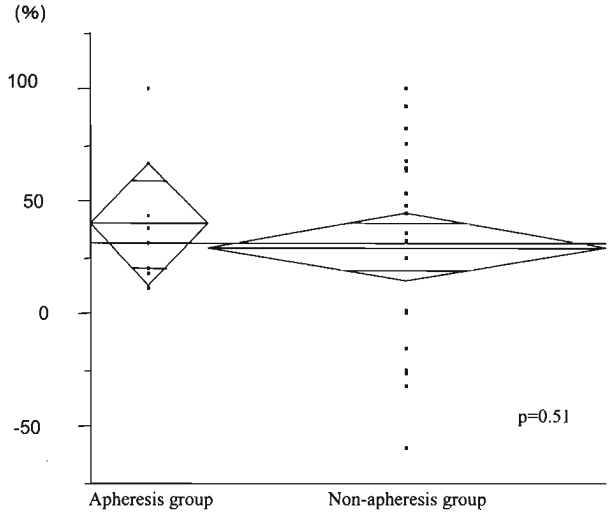

Fig. 1 Proteinuria reduction rate 8 weeks after starting treatments
As compared with the time of admission, the apheresis and non-apheresis groups demonstrated reductions in proteinuria levels, with no significant difference in those rates (p = 0.51).

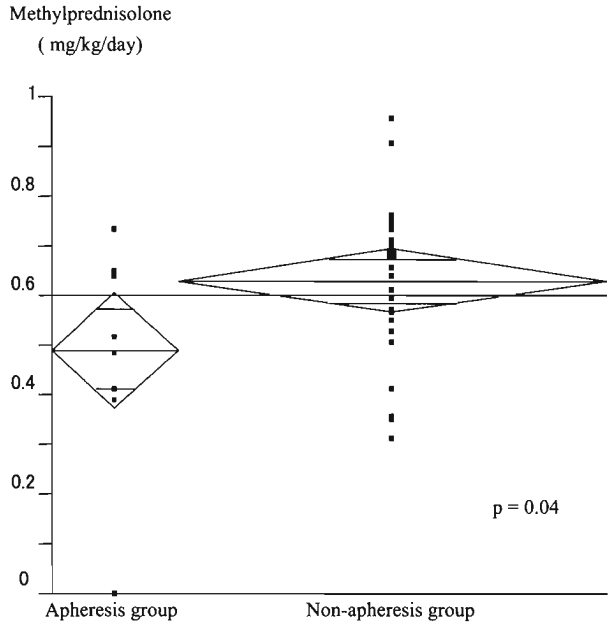

Fig. 2 Total steroid dosage for 8 weeks per 1 kg per day
In each group, the rate of patients who received steroid pulse therapy against those who did not, did not differ significantly. The dose was evaluated with the amount excluding the pulse.

time of admission, the apheresis and non-apheresis groups demonstrated reductions in proteinuria levels, i.e. 40.6±27.7% and 30.3±44.0% with no significant difference in those rates (p=0.51). Total steroid dosage for 8 weeks per 1 kg per day is provided in

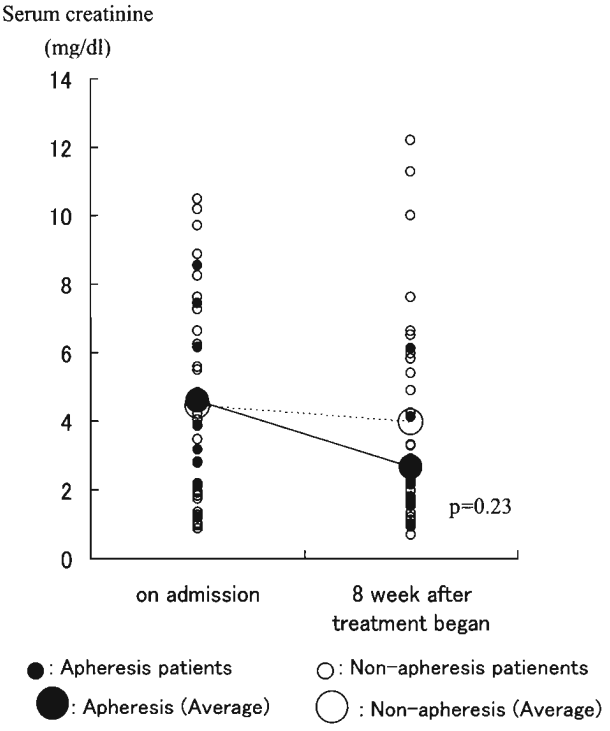

Fig. 3 Serial changes of serum creatinine levels 8 weeks after treatment
Large circles show average of serum creatinine in each group. Small circles show individual serum creatinine level. Large black circle shows that the average serum creatinine level tends to be decreased (p = 0.23).

Fig. 2. In each group, the rate of patients who received steroid pulse therapy against those who did not, did not differ significantly (6/9 patients of the former group, 17/30 patients of the latter it ; p= 0.59, χ^2 test). The dose was evaluated with the amount excluding the pulse. As shown in Fig. 2, it was 0.49±0.22 mg/kg/day in the former, and 0.63± 0.16 mg/kg/day in the latter, indicating a significantly smaller steroid dose in the apheresis group (p= 0.04). Fig. 3 shows serial changes of serum Cr levels. In the apheresis group, serum Cr tended to improve more than in the non-aphresis group (p= 0.23).

Table 3a shows renal prognosis 8 weeks after starting treatments, and Table 3b life prognosis. There were 17/30 patients who needed hemodialysis during the process in the non-apheresis group. Of these 6 withdrew from hemodialysis, but 11 needed on going treatment. On the other hand, in the apheresis group, 3/9 initially needed hemodialy-

Table 3 Renal prognosis 8 weeks after starting treatments

a: Outcome of renal death after 8 weeks			
	Renal death	Survival	Total
Apheresis group	0	9	9
Non-apheresis group	11	19	30
	11	28	39
b: Outcome of death after 8 weeks			
	Death	Survival	Total
Apheresis group	0	9	9
Non-apheresis group	3	27	30
	3	36	39

sis, but all later withdrew. In the non-apheresis group, 3 died and their initial diagnosis was MPO-ANCA associated disease. The causes of the death were 2 infections, and 1 gastrointestinal hemorrhage. None of the apheresis group patients died.

As for histological examination, the renal biopsy rate was 7/9 in the apheresis group (77.8%) and 22/30 (66.7%) in the non-apheresis group. The number of glomeruli was 20.6±14.7 in the former and 25.8±18.4 in the latter group, and neither the rate of crescent formation (73.7±16.7% in the former and 63.7±31.1% in the latter) not that of glomerulosclerosis (28.8±26.3% in the former, and 33.2±29.5% in the latter) differed significantly the between the two.

Furthermore, among the ANCA positive patients in the apheresis group, the ANCA titer after conducting apheresis was 116.8±137.7 IU/I, resulting in a rapid reduction in comparison to the amount on admission (368.6±315.9 IU/I). As compared to the non-apheresis group 8 weeks after starting treatment, it was 106.6±155.4 IU/I, p=0.89, not a statistically significant difference.

Multivariate analyses were performed to examine if apheresis was a useful predictor for improvement of serum Cr as selecting dependent variables for age, sex, proteinuria, MPO-ANCA titer, CRP, steroid pulse therapy and total steroid doses. Plasma exchange was a significant predictor for improvement of serum Cr (p=0.0068), while not in age (p=0.855), sex (p=0.915), proteinuria (p=0.1335), MPO-ANCA titer (p=0.680), CRP (p=0.245), steroid pulse therapy (p=0.478) and total steroid doses (p=0.5774).

The final outcome of RPGN was judged at 6 months after starting treatment. There were 11 of 30 patients in the non-apheresis group needed hemodialysis. On the other hand, no patients in the apheresis group needed on going hemodialysis.

Discussion

RPGN, if not treated, will proceed to end-stage renal disease in several weeks or months[2]. In an attempt to improve RPGN prognosis, it is important to diagnose the types of renal dysfunction immediately and to start prompt treatment. However, vasculitis, which accounts for most RPGN may progress rapidly and there is not enough time to wait for the results of serological tests or renal biopsy in many cases. Furthermore, many patients are elderly, and there are dangers such as fatal complications involving infections with immunosuppression. We should thus be cautions in starting this therapy. In case given steroids, it is advisable to start this treatment after diagnosing the clinical state including histological findings and serological tests.

Although apheresis is associated with, such complications as blood pressure depression accompanied by extracorporeal circulation or allergy to blood preparations used for exchanging with plasma and anti-coagulation, there is little risk of side effects as compared to using steroids[4]. There are various opinions on treatment effects for RPGN. In anti-GBM antibody-nephritis, apheresis efficacy has been reported based on reductions in serum anti-GBM antibodies and the serum Cr level, and even reduction of progression to terminal renal insufficiency, etc., as shown by randomized control trials (RCT) conducted by Johnson et al[5] and several other studies. The treatment guidelines of crescentic nephritis by the European Vasculitis Study Group recommend plasma exchange for cases with serum Cr 600 μmol/L or accompanying lung lesions. In Japan's RPGN treatment guidelines, immunosuppressant treatment is adopted according to the clinical state for ANCA-associated disease, and apheresis is not included therein.

Table 4 shows studies of the efficacy of apheresis therapy in RPGN identified by a through literature

Table 4 Studies of the efficacy of apheresis therapy in RPGN identified by a through literature search

Author	Year	Type of study	Case	Patient's disease	Apheresis	Results
Mauri[10]	1985	RCT	22	CN	PE	Benefit on serum creatinine
Glockner[7]	1988	RCT	26	CN	PE	No benefit for renal function and survival
Rifle[11]	1990	RCT	14	unknown	unknown	Benefit on renal survival
Pusey[6]	1991	RCT	48	WG, MPA, CN	PE	Benefit on renal function, but no benefit on survival
Cole[8]	1992	RCT	32	CN	PE	No benefit for renal survival and survival
Furuta[12]	1998	RCT	24	CN	LCAP	Benefit on serum creatinine
Matic[19]	2001	case series	3	WG 2, Anti GBM 1	IA	Benefit
Zauner[9]	2002	RCT	23	RPGN	PE	No benefit
Frasca[14]	2003	NRCT	26	WG, MPA	PE	Benefit on death
Nakamura[15]	2004	NRCT	22	MPO-ANCA AD	DFPP	Benefit on death
Hasegawa[16]	2006	case series	21	MPO-ANCA AD	GCAP, LCAP	Benefit for complications, renal function recovered in 76.5%
Jayne[13]	2007	RCT	137	ANCA AD (WG, CN)	PE	Benefit on renal survival

RCT: randomized controlled trial, NRCT: non-randomized controlled trial, CN: crescentic glomerulonephritis without Anti-GBM nephritis, WG: Wegener's granulomatosis, MPA: microscopic polyangitis, RPGN: rapidly progressive gromerulonephritis without Anti-GBM nephritis, MPO-ANCA AD: MPO-ANCA associated disease, PE: single plasma exchange, LCAP: leukocytapheresis, IA: immunoadsorption, DFPP: double filtration plasmapheresis, GCAP: granulocytapheresis.

search. Pusey et al[6] evaluated 48 cases and divided them into a pharmacotherapy group and a group receiving a combination of plasma exchange and drugs, based on renal functions. Although the rate of weaning from dialysis was high in the apheresis group, life prognosis was poorer than that of the pharmacotherapy group. Glocker et al[7] reported RCT in 26 cases and who showed no significant difference in death rates from dialysis weaning by plasma exchange. The report by Cole et al[8] started that the rate of dialysis weaning was same and that there were 2 deaths in the plasma exchange group but none in the control group. Zauner et al[9] reported that the HD weaning rate was the same. However, Mauri et al[10] reported in 22 RCT cases that there was a significant improvement in renal functions of cases with serum Cr levels exceeding 800 μmol/L. Rifle et al[11] and Furuta et al[12] reported in 24 RCT cases that serum Cr levels had decreased significantly with lymphocytapheresis. Jayne et al[13] reported that the rate of dialysis weaning was better in the plasma exchange group. In case series, Frasca et al[14] studied 26 ANCA positive cases and reported that the rate of dialysis weaning was better during the acute phase and there were fewer deaths in the plasma exchange group. Nakamura et al[15] reported a reduction in urinary podocytes and no deaths in the plasma exchange group. Hasegawa et al[16] conducted granulocytapheresis and leukocytaphereis on 21 MPO-ANCA positive cases, and serum Cr levels improved in 13 of the 17 responsive cases. As shown here, many reports describe improvements in renal functions while discussing evaluations of prognosis.

In our retrospective studies, we found improvements in both life and renal prognosis with apheresis therapy, finding not reported previously. Considering the state usually requiring hemodialysis as complete renal failure, the number of such cases was significantly reduced in the apheresis group. As for life prognosis, the long-term prognosis was not evaluated (On-dialysis cases or patients who changed hospitals due to moving could not be traced.). However, the evaluation done after 8 weeks, when a stable state had returned, after surviving the acute phase with the highest death rate for vasculitis, is considered to be quite valuable. In fact, we studied traceable cases and found that patients were off dialysis and alive for at least 2 years afterwards.

We studied creatinine clearance, and serum Cr levels for the evaluation of renal functions on admission in both groups, albumin levels for the evaluation of nutrition, hematuria for the evaluation of vasculitis, and CRP and leukocyte levels for the evaluation of inflammatory state, We detected no differences between the two groups. Their systemic states were considered to be similar. Only the

proteinuria level was higher in the apheresis group. If proteinuria is considered to be an index of renal dysfunction, the apheresis group has more aggressive renal injury than the non-apheresis group. Reduction rates of proteinuria after 8 weeks were evaluated,as shown in Fig. 1. Reduction of proteinuria was to 40.6±27.7% in the apheresis group vs 30.3±44.0% in the non-apheresis group, not a significant difference. We compared therapy results based on total steroid doses for 8 weeks (Fig. 2). The apheresis group showed significantly lower amount, i.e. had the same reduction in proteinuria as the non-apheresis group receiving lower steroid doses.

Furthermore, there were no renal deaths or any other deaths in the apheresis group (Table 3a, b). Although the two groups did not differ in serum Cr level or creatinine clearance on admission, all 3 HD patients in the apheresis group were weaned from dialysis, while 11 of 17 patients in the non-apheresis group were maintained on dialysis. There were 3 deaths in the non-apheresis group, of whom 2 (due to infection) were considered to have been affected by immunosuppressant side effects. Steroid therapy plays an important role in RPGN, but its side effects are often fatal and severe, e.g gastrointestinal hemorrhage, infection, etc. Lower total steroid doses are considered to be a reason for the improved prognosis in the apheresis group. Our present study is the first to show that both renal and life prognoses are better in RPGN patients receiving apheresis combination therapy.

The principle of apheresis utility has yet to be resolved, and there are reports describing depletion of immune complexes or inflammatory mediators[17], i.e immunoreactive modifications[18)19)]. Herein, we cannot rule out the possibility of rapid and considerable reductions in ANCA titers with apheresis. We considered apheresis to decrease immune complexes, the inflammatory factors determining treatment efficacy in ANCA negative RPGN patients. Therefore, apheresis was effective in cases with and without ANCA.

As to the primary diseases, ANCA rates were higher in both groups (Table 1). The primary disease causing the 3 deaths was ANCA-associated disease. There were no deaths in the apheresis group probably because of the low number of ANCA-associated disease cases. However, there was no difference in systemic state on admission and progress after admission between the two groups (Table 2). This result is considered to be valuable, though BVAS scores were not compared due to the retrospective nature of the study[20]. Comparing only ANCA-associated disease cases, rapid and remarkable ANCA titer reductions after apheresis were seen in our study as well. The evaluation at 2 months after starting therapy showed no difference in ANCA titers between the two groups, and that each group showed significant reductions. There are no reports indicating that lowering ANCA in blood may rapidly lead to the improvements in disease activity and the relation between the absolute ANCA titer and disease conditionsis not clear. Even though ANCA is the first sign of vascular endothelial dysfunction, reducting ANCA in the early stage of disease is very meaningful. Apheresis can directly eliminate pathogenic factors in plasma until the efficacy of immunosuppressants, including steroids, manifests during the acute phase. Immunosuppressive therapy is greatly enhanced by apheresis. Certain reports have recommended combined use of apheresis for cases with high serum Cr levels or for RPGN cases on dialysis. In our study, there were no significant differences in serum Cr level on the whole, and 3/9 patients in the apheresis group needed dialysis on admission, while 17/30 in the non-apheresis group required dialysis. The results indicate that apheresis in the early phase is effective, depending on individual patient status, even for cases in whom renal function had not deteriorated at the beginning of the therapy.

There were a few limitations in our study. The study was a retrospective analysis with a short term observation period. Therefore, we should be careful to interpret the efficacy of apheresis on the clinical outcomes in patients with RPGN. However, the final outcome of RPGN patients in apheresis group needed on going hemodialysis 6 months after starting treatment.

Conclusions

Both renal and life prognoses were better in the apheresis group in treating RPGN patients. The total steroid dose for 2 months after admission was lower in the apheresis group, and the improvements in proteinuria were similar to those of the non-apheresis group. As there are fewer cases in the apheresis group, we should accumulate more cases and repeat the evaluation.

Acknowledgements

The authors thank Prof. Takashi Akiba for his critical assessment of the manuscript. This work was partly supported by a Grant-in-Aid from Japan Ministry of Health, Welfare and Labor.

References

1) **Churg J, Bernstein J, Classock RJ**: Classification of glomerular diseases. *In* Renal Disease 2nd ed. World Health Organization (WHO) Monograph, pp3–23, Igaku-Shoin Medical Publichers (1995)
2) **Couser WG**: Rapidly progressive glomerulonephritis. Classification, pathogenic mechanisms, and therapy. Am J Kidney Dis **11**: 449–464, 1988
3) **Sakai H, Kurokawa K, Koyama T et al**: Clinical guideline for rapidly progressive glomerulonephritis in Japan. Jpn J Nephrol **44**: 55–82, 2002 (in Japanese)
4) **Basic-Jukic N, Kes P, Glavas-Boras S et al**: Complications of therapeutic plasma exchange: Experience with 4857 treatments. Ther Apher Dial **9**: 391–395, 2005
5) **Johnson JP, Moore JJ, Austin HA, 3rd et al**: Therapy of anti-glomerular basement membrane antibody disease: analysis of prognostic significance of clinical, pathologic and treatment factors. Medicine **64**: 219–227, 1985
6) **Pusey CD, Rees AJ, Evans DJ et al**: Plasma exchange in focal necrotizing glomerulonephritis without anti-GBM antibodies. Kidney Int **40**: 757–763, 1991
7) **Glockner WM, Sieberth HG, Wichmann HE et al**: Plasma exchange and immunosuppression in rapidly progressive glomerulonephritis: a controlled multi-center study. Clin Nephrol **29**: 1–8, 1988
8) **Cole E, Cattran D, Magil A et al**: A prospective randomized trial of plasma exchange as additive therapy in idiopathic crescentic glomerulonephritis. Am J Kidney Dis **20**: 261–269, 1992
9) **Zauner I, Bach D, Braun N et al**: Predictive value of initial histology and effect of plasmapheresis on long-term prognosis of rapidly progressive glomerulonephritis. Am J Kidney Dis **3**: 28–35, 2002
10) **Mauri JM, Gonzales MT, Poveda R et al**: Therapeutic plasma exchange in the treatment of rapidly progressive glomerulonephritis. Plasma Ther Transfus Technol **6**: 587–591, 1985
11) **Rifle G, Dechelette E**: Treatment of rapidly progressive glomerulonephritis by plasma exchange and methylprednisolone pulses. A prospective randomized trial of cyclophosphamide. Interium analysis. The French Cooperative Group. Prog Clin Biol Res **337**: 263–267, 1990
12) **Furuta T, Hotta O, Yusa N et al**: Lymphocytapheresis to treat rapidly progressive glomerulonephritis: a randomized comparison with steroid-pulse treatment. Lancet **352**: 203–204, 1998
13) **Jayne DRW, Gaskin G, Rasmussen N et al**: Randomized trial of plasma exchange or high-dosage methylprednisolone as adjunctive therapy for severe renal vasculitis. J Am Soc Nephrol **18**: 2180–2188, 2007
14) **Frasca G, Soverini M, Falaschini A et al**: Plasma exchange treatment improves prognosis of antineutrophil cytoplasmic antibody-associated crescentic glomerulonephritis: a case-control study in 26 patients from a single center. Ther Apher Dial **7**: 540–546, 2003
15) **Nakamura T, Matsuda T, Kawagoe Y et al**: Plasmapheresis with immunosuppressive therapy vs immunosuppressive therapy alone for rapidly progressive anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis. Nephrol Dial Transplant **19**: 1935–1937, 2004
16) **Hasegawa M, Ohashi A, Kabutan N et al**: Cytapheresis for the treatment of myeloperoxidase antineutrophil cytoplasmic autoantibody-associated vasculitis: a pilot study of 21 patients. Ther Apher Dial **10**: 412–418, 2006
17) **Lockwood CM, Punching AJ, Sweny P et al**: Plasma exchange and immune suppression in the treatment of fulminating immune complex crescentic nephritis. Lancet **1**: 63–67, 1997
18) **Steven MM, Tanner AR, Holdstock GE et al**: The effect of plasma exchange on the in vitro monocyte function of patients with immune complex disease. Clin Exp Immunol **45**: 240–245, 1981
19) **Matic G, Michelsen A, Hofmann D et al**: Three cases of C-ANCA-positive vasculitis treated with immunoadsorption: possible benefit on early treatment. Ther Apher **5**: 68–72, 2001
20) **Luqmani RA, Bacon PA, Moots RJ et al**: Birmingham Vasculitis Activity Score (BVAS) in systemic necrotizing vasculitis. QJM **87**: 671–678, 1994

急速性進行性糸球体腎炎の治療における血漿交換療法

[1]東京女子医科大学医学部第四内科学（主任：新田孝作教授）
[2]東京女子医科大学腎臓病総合医療センター血液浄化療法科
[3]自治医科大学腎臓内科
赤尾　正恵[1]・内田　啓子[1]・菊地　勘[2]・湯村　和子[3]・新田　孝作[1]

急速進行性糸球体腎炎（rapidly progressive glomerulonephritis；RPGN）の治療において，副腎皮質ステロイド薬などの免疫抑制薬が第一選択であるが，血漿交換療法（plasma exchange；PE）も治療の一環として施行されることがある．本研究の目的は，RPGNの治療におけるPEの有効性を検討することである．我々は1995～2005年までの10年間で，39例のRPGNに対する治療法に関して，PE施行群とPE未施行群に分けて，後ろ向きに検討した．1例を除けば，全例で副腎皮質ステロイド薬の投与を受けていた．PE施行群の9例では，二重膜濾過あるいは単一膜血漿交換法による治療を，2～7回に渡って施行されていた．両群間における腎機能と炎症マーカーには有意差を認めなかった．治療開始時の尿蛋白量は，PE施行群で3.4±2.5 mg/dl（0.38～6.44 g/日），PE未施行群では1.5±1.4 mg/dl（0.12～5.58 g/日）で有意差を認めた（p＝0.007）．しかし，治療期間中の総ステロイド投与量は，PE未施行群の0.63±0.16 mg/kg/日に対して，PE施行群では0.49±0.22 mg/kg/日と有意に少なかった（p＝0.04）．両群の腎機能と予後は，PE未施行群に比しPE施行群で良好であった．これらの結果から，RPGNの治療においては，免疫抑制薬とPEの併用により，腎保護と予後の改善が期待できると考えられた．