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ORIGINAL COMMUNICATION

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Comparison between double-filtration plasmapheresis and immunoadsorption plasmapheresis in the treatment of patients with myasthenia gravis

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Abstract Two techniques for plasmapheresis are used in the treatment of myasthenia gravis (MG): immunoadsorption (IA) and double filtration (DF). This controlled study evaluated the differences between these techniques in clinical effects and serological changes. Five patients with generalized MG (clinical states IIb and III) were enrolled; each patient received IA and DF plasmapheresis on separate occasions. Immunosorba TR–350 with an affinity to acetylcholine receptor antibodies (AchRAb) was used for IA, while Evaflux 4A was used as the plasma fractionator for DF. Each course of treatment consisted of five sessions of apheresis. MG score, titers of AchRAb, immunoglobulins (Ig), and plasma biochemistry were assessed by blinded examiners before and immediately after the entire course of treatment. Both treatments effectively ameliorated symptoms of MG. There were no significant changes in MG score between the two groups (IA vs. DF: 2.2 vs. 2.6, $P > 0.5$). IA had a higher clearance rate of AchRAb than DF (66 % vs. 54 %, $P < 0.05$), while DF removed more IgA (72 % vs. 21 %, $P < 0.05$) and IgM (89 % vs. 57 %, $P < 0.01$) than did IA. Although IA removed AchRAb more effectively than DF, the clinical effects between these two treatments were similar. The titers of AchRAb cannot reflect the clinical severity. Some circulating factors other than AchRAb may contribute to the pathogenesis of MG.

Key words Double filtration plasmapheresis · Immunoadsorption plasmapheresis · Plasma exchange · Myasthenia gravis · Acetylcholine receptor antibody

Introduction

Circulating antibodies to acetylcholine receptor (AchR) are detectable in most patients with generalized myasthenia gravis (MG) [5]. Plasma exchange (PE) has been shown to induce a rapid recovery, corresponding to the decline in AchR antibodies (AchRAb) [9]. However, major drawbacks of plasma exchange are the need for plasma supplements and the possible risk of allergic reaction and transfusion-related infection [4, 16]. In recent years newly developed techniques for plasmapheresis, including double filtration plasmapheresis (DF) [1] and immunoadsorption plasmapheresis (IA) [18], provide more selective removal of pathogenic substances without the need for plasma supplementation.

DP consists of a first filter to separate plasma from blood (a plasma separator) and a second filter to separate albumin from larger molecules, such as immunoglobulins, immune complexes, and lipoproteins in the plasma (a plasma fractionator). Yamazaki et al. [18] developed an IA therapy using an affinity-type adsorbent of tryptophan-linked polyvinyl alcohol gel that selectively adsorbs most large proteins, including most AchRAb through hydrophobic interaction. The clinical response rate of the two methods is approximately the same, around 70–90 % [2, 7, 8, 11,

13, 15, 19, 20]. However, there has as yet been no objective comparison between these two methods. Therefore we compared the efficacy and safety of the DF and IA methods in this study.

Materials and methods

Five patients were studied (three men, two women; aged 35–69 years) who were affected by severe generalized or respiratory MG, with an Osserman's classification of group 2 or 3, and who had not responded to previous treatments (Table 1). All but one patient had been on immunosuppressant therapy. All had undergone thymectomy. Each patient received DF treatment at the first episode of clinical deterioration. IA treatment was reserved for the subsequent relapse of myasthenic weakness. The interval between DF and IA ranged from 4 months to 2 years. Clinical status and AchRAb titer did not differ between pre-DF and pre-IA states. Evaflux 4A (Kuraray, Osaka, Japan) was used as the plasma fractionator for DF, while Immunosorba TR–350 (Asahi Medical, Tokyo, Japan) was used for IA. Each course of treatment consisted of five sessions of apheresis on alternate days with one plasma volume processed. Either a double-lumen catheter in a central vein (four patients) or an arteriovenous shunt (one patient) was used for vascular access. Heparin was used as the anticoagulant. No replacement fluids were given. All medication had remained unchanged for 6 months prior to plasmapheresis.

Patients were evaluated by a modified MG score before and after the entire course of plasmapheresis [20]. The score was calculated as the sum of the grades for six items, including duration of outstretched time of both arms and legs, vital capacity, functional grading of facial muscles, chewing, and swallowing. Each item was graded on a scale of 0 (normal) to 3 (severe paralysis). An MG score of 0 indicated normal status and 18 maximal weakness. The clinical evaluation was made independently by a research nurse who was unaware of the details of plasmapheresis treatment.

Blood was collected before and after treatment in both methods to measure serum albumin, globulin, immunoglobulins G, A, and M, and AchRAb. The AchRAb titer was measured using a standard radioimmunoassay by a AchRAb kit (RSR, UK) [19]. We incubated 5 µl serum, 50 µl AchR, and 50 µl anti-human IgG were incubated overnight at 4°C. The removal rate of serum proteins and AchRAb during plasmapheresis was calculated as: [(pre-plasmapheresis concentration–post-plasmapheresis concentration)/(pre-plasmapheresis concentration)]. Serological changes between groups were compared using the Mann-Whitney *U* test.

Results

Both treatments effectively ameliorated symptoms of MG. Figure 1 shows the changes in MG score after treatment. The mean reduction in MG score was 2.6 points in the DF group and 2.2 in the IA group. The degree of improvement in muscle strength was not significantly different between the groups. Figure 2 shows the serological changes after plasmapheresis. The IA method had a higher clearance rate of AchRAb than DF (66 % vs. 54 %, $P< 0.05$), while the DF method removed more IgA (72 % vs. 21 %, $P< 0.05$) and IgM (89 % vs. 57 %, $P< 0.01$) than the IA method (Fig. 2). The decrease in albumin was lower than that of the other proteins. No instance of hypotension was observed in the 25 sessions (five cases in five sessions). There was one incident of catheter-related infection in the IA group. No allergic response or post-plasmapheresis infection was found.

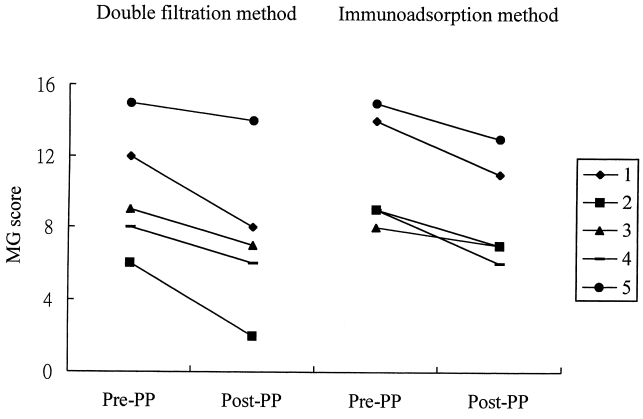

Fig. 1 Changes in myasthenia gravis (*MG*) score after plasmapheresis (*PP*) with the double-filtration or immunoadsorption methods

Table 1 Patient profile (*Pre-PP* before plasmapheresis, *MG* myasthenia gravis, *AchRAb* acetylcholine receptor antibody)

Patient no.	Sex	Age (years)	Thymic pathology	Clinical grade[a] DF	IA	Pre-PP MG score DF	IA	Pre-PP AchRAb DF	IA	Immunosuppressants (mg/day) Prednisolone DF	IA	Azathioprine DF	IA
1.	F	35	Hyperplasia	IIb	IIb	12	14	9.9	5.0	30	30	100	100
2.	M	69	Atrophy	IIb	IIb	6	9	9.2	11.3	30	0	100	100
3.	M	63	Thymoma	IIb	IIb	9	8	86.3	68.9	0	0	50	100
4.	M	41	Thymoma	III	III	8	9	22.7	54.1	15	0	0	0
5.	F	40	Hyperplasia	III	III	15	15	54.8	78.1	30	30	0	0

[a]Osserman's classification

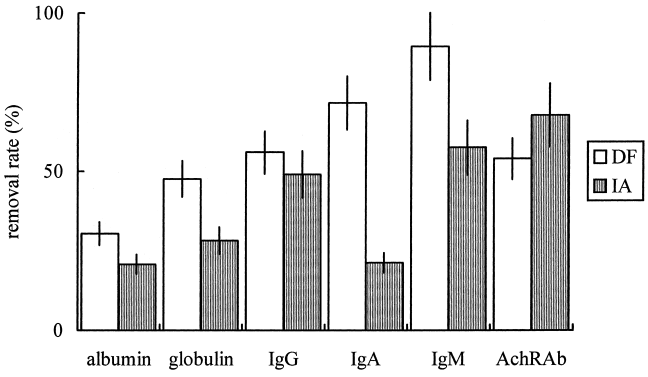

Fig. 2 Mean removal rate for serum proteins, immunoglobulins (*Ig*), and acetylcholine receptor antibody (*AchRAb*) with double-filtration (*DF*) and immunoadsorption (*IA*) plasmapheresis

Discussion

Newly developed techniques of DF and IA plasmapheresis provide more selective removal of pathogenic factors via the mechanisms of filtration or antigen-antibody adsorption, respectively, than the nonselective replacement of total plasma in plasma exchange. The clinical efficacy of DF or IA in the management of MG was approximately the same as plasma exchange in analyses of reported studies [7, 20]. Variations in clinical response can be due to methodological differences in the choice of plasmapheresis protocol, the homogeneity of subjects, and the definition of clinical response. However, there has not been an objective comparison between these methods.

Although IA removes AchRAb more effectively than DF, clinical effects between these two treatments are similar. AchRAb titers cannot reflect the clinical severity, and a change in clinical state may occur without a detectable change in titer [12]. Immune complexes that were directly demonstrated at the motor endplate in both experimental and human MG have also been suggested as contributing to AchR deficiency [2, 6]. Moreover, some undetected mediators or antibodies, including extra-autoantibodies other than AchRAb (i. e., ryanodine receptor antibodies and titin antibodies) not detected by standardized immunoprecipitation assays are presumed to contribute to the muscular weakness in seronegative MG on the basis of clinical improvement with plasmapheresis [10, 14]. Blocking antibodies, which pharmacologically block the receptor function with less affinity to AchR than that of binding antibody, play a role in the pathogenesis of myasthenic weakness [3, 17]. Therefore the extent and reversibility of the morphological change in AchR, the level of complement activation, and polyclonal epitopes of AchRAb are thought to be associated with the discrepancy between the clinical and serological status [12]. In our study we also identified a discrepancy between the change in AchRAb level and clinical status.

A major disadvantage of plasma exchange is the unselected removal of all plasma proteins, which requires replacement with human proteins. The inherent and potential risks of replacement fluid include anaphylactic reactions and transfusion-transmitted infection such as hepatitis and human immunodeficient virus infection [4]. DF and IA are free of these transfusion-related complications. In this study, vascular access-related complications were the most common complications of plasmapheresis. These are common to any kind of extracorporeal circulation procedures.

The DF method removes some circulating pathogenic factors other than AchRAb and is a simple and inexpensive therapeutic tool that exhibits performance comparable to that of the IA method in treating patients with severe generalized MG.

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