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Plasma-Separation in Myasthenia Gravis: A New Method of Rapid Plasma Exchange *

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Plasmaseparation bei Myasthenia gravis: Eine neue Methode für einen raschen und effektiven Plasmaaustausch

Zusammenfassung. Bei einer Patientin mit einer myasthenischen Krise wurde erstmals ein neuartiges Verfahren zur Plasmapherese angewandt. Dabei erfolgte die Plasmaseparation mittels eines Membranfilters in der Form eines Hohlfaserbündels. Der hierbei erforderliche apparative Aufwand ist erheblich geringer als bei den bisher zum Plasmaaustausch verwandten Blutzellseparatoren. Das neue Verfahren erscheint geeignet, der Plasmapherese zu einer weiten klinischen Anwendung zu verhelfen.

Schlüsselwörter: Plasmaseparation – Myasthenia gravis – Anti-Acetylcholin-Rezeptor-Antikörper

Summary. A patient with myasthenic crisis was successfully treated with a new method of plasma exchange using a hollow-fiber filter connected to a standard dialysis pump. The filter allows PE to be performed at more clinical centers and probably at lower costs than current methods applying blood cell separators.

Key words: Plasma separation – Myasthenia gravis – Anti-acetylcholine receptor antibodies

Circulating antibodies directed against the acetylcholine receptor (ACh-R) at the neuromuscular junction are probably the main cause of the transmission defect in myasthenia gravis (MG) [2, 5, 12]. Clinical improvement of patients associated with elimination of immunoglobulins (Ig) by plasma exchange (PE) has confirmed the pathogenetic role of anti-ACh-R antibodies [1, 6, 9]. In this study, we report on a new and rapid method of plasma exchange using a special hollow-fiber filter allowing the exchange of macromolecules.

The filter was previously used as an artificial liver support system [8, 13], for treatment of intractable ascites [3] and as a new method for plasma exchange in Goodpasture's syndrome, hyperproteinemic coma and digitalis poisoning [10].

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Method

The hollow-fiber filter (Plasmaflo™)[1] consists of Cellulose-di-acetate with a wall thickness of 160 µm, an effective surface area of 0.65 m^2, and a maximum pore size of 0.2 µm with an upper cut off of approximately 3,000,000 Daltons.

At a blood flow of 100 ml/min, about 30 ml plasma/min can be separated. This separated fluid contains about 60% of the protein amount of the patient's plasma. Albumin as well as immunoglobulins (IgG, IgA, IgM) pass through the filter. No loss of erythrocytes, leucocytes or thrombocytes was observed during a 2 liter exchange.

The plasma separation can be carried out by arterio-venous or veno-venous pathways, corresponding to conventional hemodialysis. The replacement fluid consists of 5% human albumin solution with proper electrolyte adjustment. Gamma globulin substitution is necessary only in some patients treated with immunosuppressive drugs.

For the application of the described plasma filter a blood pump is attached to the arterial tubing and the replacement fluid is added into the venous line. Before retransfusion, the blood should be rewarmed to 37° C. At least 5,000 units of heparin are needed for anticoagulation. Using a simple bed side clotting test, the coagulation time should be more than 15 min.

Case Report

A 20-year-old female patient (L.M.) had developed signs of moderately severe MG one year prior to PE. The tensilon test was positive and a 52% decrement was seen on repetitive nerve stimulation ($2 \cdot s^{-1}$) at the deltoid muscle. Vital capacity was 2.0 liters and increased to 2.7 liters after 0.5 mg of physostigmine i.v. No thymoma was found on standard x-ray and on computerized tomography of the anterior mediastinum. Antibodies against skeletal muscle (indirect immunofluorescence method) were negative. Thyroid function tests were normal.

The initial concentration of antibodies against human ACh-R was 590 nmoles ^{125}I-alpha-bungarotoxin binding sites/liter serum (normal < 0.4 nmoles) using an immunoprecipitation assay [4] with slight modifications [11].

[1] Asahi Medical Co., Ltd., Tokyo, Japan

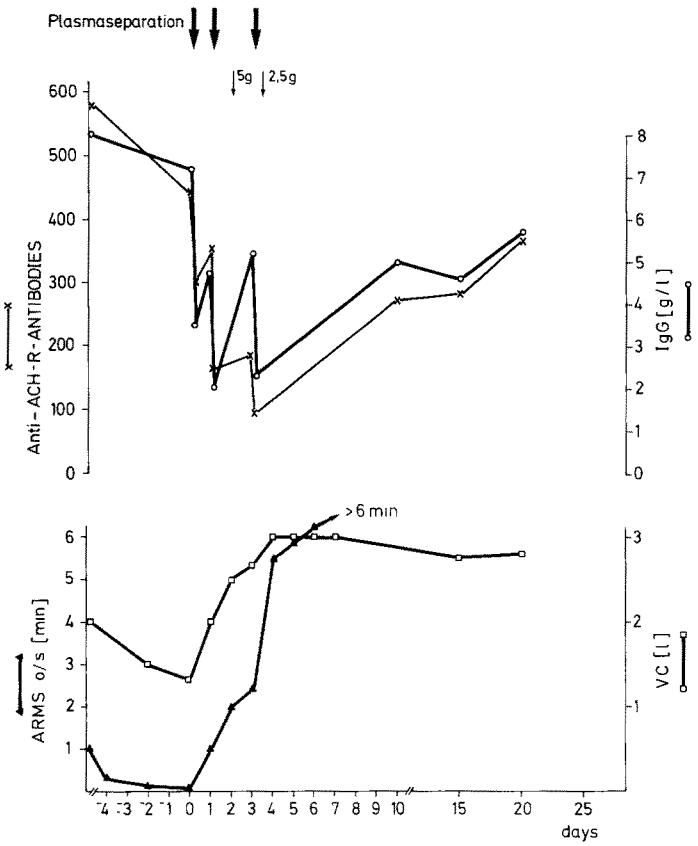

Fig. 1. Clinical signs, serum anti-ACh-R antibody titers (nmoles ^{125}I-alpha-bungarotoxin binding sites/l) and IgG concentrations during treatment of myasthenic crisis with plasma exchange. Large arrows indicate time of exchange (2 liters each), small arrows indicate replacements of IgG. *VC* vital capacity; *ARMS o/s* time for which arms could be held outstretched against gravity

Muscle strength improved after initiation of pyridostigmine bromide (60 mg p.o. every 4 h) and oral prednisone was started with 25 mg/day up to 50 mg/day within six days. First signs of amelioration were seen at the extraocular muscles ten days later. After twenty-one days the generalized muscle weakness worsened progressively over five days despite optimal adjustment of anticholinesterase treatment and the patient developed myasthenic crisis. She was not able to lift her arms or swallow, and the vital capacity was only 1.3 liters. No obvious reason except a possible late adverse effect of the corticosteroid treatment could be evaluated. It was decided to treat this patient with a series of PE, for the first time using a new hollow-fiber filter instead of an Aminco Celltrifuge that had been applied in previous patients.

Vessel access was performed by means of an external arteriovenous (Scribner) shunt on the left forearm. For anticoagulation, 5,000 units of Heparin were required and 2 liters of plasma were exchanged per session. The fluid replacement was carried out as described above. After the second PE, 5 g of gamma globulin and after the third PE, another 2.5 g were given i.v. During the course of PE and up to three weeks later, serial measurements of the vital capacity and the length of time that the arms could be held against gravity were made.

Repeated PE with a hollow-fiber filter caused marked improvement of the clinical state and a decrease in anti-ACh-R antibody titers to 21% of the original value (Fig. 1). Serum electrolytes remained within the normal range. After the series of 3 PE, the antibody titers rose to almost 62% of the preexchange values over the following twelve days. Total IgG returned towards normal values at about the same rate after the last PE.

Clinical improvement started with a time lag of six hours after each PE, and reached maximal values on the sixth day. After the second PE, the dosis of anticholinesterase could be tapered gradually from 0.5 mg of physostigmine/hour i.v. to 60 mg of pyridostigmine every 4 h p.o. After the sixth day following the first PE, no significant change in clinical weakness was observed.

Discussion

The usefulness of plasma exchange as an adjunct to immunosuppressive drug treatment has recently been established [1, 6, 7, 9]. PE has been advocated for patients who are resistant to conventional medical treatment and for acute myasthenic crisis to allow rapid elimination of the pathogenic anti-ACh-R antibodies. The feasibility of PE as a means of emergency treatment in myasthenic crisis is limited by the fact that only few large medical centers have access to a blood cell separator. The new hollow-fiber filter, however, which for additional equipment requires only a blood pump and a rewarming bath, is extremely small, portable and easy to handle. Furthermore, such a unit can be used at any place where there is experience with the technique of extracorporal circulation. The investment costs for this device are considerably lower than for conventional plasma separators although the costs of disposable apparatus at each exchange are at present higher.

Compared to previous studies using Hemonetics of Celltrifuge blood cell separators [1, 6, 7, 9], the hollow-fiber filter appears to be as efficient in eliminating antibodies. No adverse reactions intrinsic to this new device have been observed. Thus, our report means to call attention to this new method that warrants further clinical testing but is not meant to stimulate the indiscriminate use of PE in MG [7].

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