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PLASMAPHERESIS AND SPECIFIC IMMUNOADSORPTION IN THE TREATMENT OF MYASTHENIA GRAVIS

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SUMMARY – Myasthenia gravis is an antibody-mediated autoimmune disease in which circulating acetylcholine receptor (AChR) antibodies have been identified that bind to the receptor sites in voluntary muscles, thereby damaging and blocking the receptors. Selective removal of the blocking antibody by plasmapheresis or specific immunoadsorption provides important methods in the treatment of patients with myasthenia gravis. Novel immunoadsorbent columns have been developed especially for the treatment of patients with myasthenia gravis, using a specific affinity ligand (*Torpedo* 183-200, a synthetic peptide) to remove the blocking antibody. This immunoadsorbent produced specific removal of the blocking antibody without reducing other plasma proteins. Clinical improvement was observed in 78% of myasthenia gravis patients. There were no adverse effects.

Key words: *Myasthenia gravis, therapy; Plasmapheresis*

Introduction

In the past 30 years, several studies have documented the effect of plasmapheresis and immunoadsorption in eliminating pathogenic autoantibodies (ABs) and immune complexes (ICs) from circulation. In almost any immune disease, extracorporeal therapy is tried in critical situations, but only in thrombotic-thrombocytopenic purpura, cryoglobulinemia, Goodpasture's syndrome, Guillain-Barre syndrome, and crisis in myasthenia gravis plasmapheresis is standard therapy[1-3].

Myasthenia gravis is a chronic disease which most commonly occurs in young adults, and progresses with remisssions and exacerbations. It is characterized by the activity-induced abnormal muscle fatigability with typical drooping of eyelids and jaw, nasal voice, slurred speech, and weakness of proximal extremities. It involves progressive failure of impulse conduction at the neuromuscular junction. Myasthenia gravis is an autoimmune disorder in which neuromuscular transmission is impaired by anti-acetylcholine receptor (AChR) antibodies. The anti-AChR antibodies involved in the pathogenesis of myasthenia gravis are classified into two subclasses: one is the blocking antibody, and the other is the binding antibody. The blocking antibody is known to directly block the acetylcholine (ACh) binding site of AChR, and this is one of the cases of myasthenia gravis. From this point of view, removal of the blocking antibody is an important method in the treatment of myasthenia gravis.

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Plasmapheresis

Plasmapheresis is a method of treatment aimed at removing AChR antibodies from the plasma to decrease the autoimmune activity. Several uncontrolled trials and numerous anecdotal reports describe dramatic post-plasmaphereis treatment results[2,4]. There has been no controlled trial with plasmapheresis in myasthenia gravis patients, nevertheless, the 1985 NIH Consensus Conference concluded that plasmapheresis might be useful in increasing muscle strength during the pre- and post-thymectomy period, and in decreasing symptoms during the initiation

of immunosuppressive therapy as well as in acute crisis[1]. Plasmapheresis was also found beneficial in four of eight patients with seronegative myasthenia gravis[5]. The possible explanation is inability of the assay to detect AChR antibody or existence of antibodies that may be directed against a different antigenic determinant of the neuromuscular junction[3].

The recommended plasmapheresis prescription is 5 treatments over a one-week period. Each treatment should equal 1.5 plasma volume (PV), which can be replaced with 5% albumin. If the patient is in the immediate prethymectomy period, partial replacement of approximately one liter of fresh frozen plasma (FFP) given toward the end of the last treatment should help reverse the expected depletion coagulopathy. Although the levels of AChR antibodies are unlikely to be observed, the expected declines in AChR antibodies reveal an excellent correction with the calculated total IgG removal kinetics[6].

Specific Immunoadsorption

Takamori et al.[7] report that the 183-200 segment of the *Torpedo Californica* AChR binding site recognized by the blocking antibody, and this *Torpedo* peptide showed a much more potent binding ability than the human peptide. Based on these studies, Miyahara et al.[8] have designed a new immunoadsorbent especially for the treament of myasthenia gravis, using *Torpedo* 183-200, a synthetic peptide, as a specific affinity ligand to remove the blocking antibody. The immunoadsorbent column (Medisorba MG column) is packed with 50 ml of porous cellulose beads covalently immobilized with the synthetic peptide and sterilized by autoclaving. The safety of the immunoadsorbent has been confirmed by various toxicity tests. The release of the peptide from the adsorbent was minimal. The adsorption performance of Medisorba MG column was firstly evaluated *in vitro* using the plasma from myasthenia gravis patients. The immunoadsorbent produced specific and significant removal of the blocking antibody without reducing IgG and albumin concentrations in an *in vitro* study. In clinical evaluation, Ide et al.[9] carried out 77 treatments of plasma perfusion in 19 myasthenia gravis patients. The removal rate of anti-AChR blocking antibody and anti-AChR binding antibody was approximately 40.2% and 12.4%, respectively. The blocking antibody was specifically removed in these immunoadsorption treatments, without any significant reduction of the plasma protein level. Clinical improvement was observed in 78% of patients with myasthenia gravis, and no adverse effects were recorded[9]. The Medisorba MG column has been confirmed as a useful tool in therapy for myasthenia gravis.

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Sažetak

LIJEČENJE MIASTENIJE GRAVIS POMOĆU PLAZMAFEREZE I SPECIFIČNE IMUNOADSORPCIJE

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Miastenija gravis je autoimuna bolest kod koje se cirkulirajuća protutijela protiv receptora za acetilkolin vežu za receptorska mjesta na poprečnoprugastim mišićima i dovode do blokiranja i oštećenja receptora. Blokirajuća protutijela mogu se specifično odstraniti iz plazme bolesnika s miastenijom gravis pomoću plazmafereze ili specifične imunoadsorpcije. Nove kolone za imunoadsorpciju u kojima se kao specifični vezač za blokirajuće protutijelo acetilkolinskih receptora rabi sintetički peptid *Torpedo* 183-200 pokazale su visoku specifičnost u odstranjivanju blokirajućih protutijela, a da pritom nisu utjecale na koncentraciju drugih bjelančevina u plazmi. Do kliničkog poboljšanja došlo je u 78% bolesnika s miastenijom gravis, a da nije zabilježena niti jedna nuspojava.

Ključne riječi: *Miastenija gravis, liječenje; Plazmafereza*