PLASMAPHERESIS IN THE TREATMENT OF MYASTHENIA GRAVIS

Retrospective study of 26 patients

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ABSTRACT - We analyzed the experience of Unicamp Clinical Hospital with plasma exchange (PE) therapy in myasthenia gravis (MG). About 17.8% of a totality of MG patients had PE performed: 26 cases, 19 women and seven men. The mean age-onset of MG was 28 years, extremes 11 and 69. Minimum deficit observed in the group was graded IIb (O & G) or IIIa (MGFA scale). One patient had prethymectomy PE. In seven the procedures were performed due to myasthenic crisis and in 18 patients due to severe myasthenic symptoms or exacerbation of previous motor deficit. Two patients were also submitted to chronic PE considering refractoriness to other treatments. Twenty-six patients had 44 cycles of PE and 171 sessions. The mean number of sessions was 3.9 (SD ± 1.4) each cycle; median 5, extremes 2 and 6. The mean time by session was 106.5 minutes (SD ± 35.2); median 100.5 (extremes of 55 and 215). The mean volume of plasma exchanged in each session was 2396 ml (SD ± 561); median 2225 (extremes 1512 and 4500). Side effects occurred: reversible hypotension (seven cases), mild tremor or paresthesias (seven cases). Infection and mortality rates due to PE were zero. All patients had immediate benefit of each PE cycle and usually they also received prednisone or other immunosuppressors. Good acceptance of the procedure was observed in 80.7% of patients.

KEY WORDS: plasmapheresis, myasthenia gravis, therapeutics, acceptance, complications.

Myasthenia gravis (MG) is a well known autoimmune disease characterized by antibodies against nicotinic acetylcholine receptors and fluctuating weakness, sometimes life-threatening1. Plasmapheresis or plasma exchange (PE) is a therapeutic modality well established in MG2 with a positive recommendation based on strong consensus of Class III evidence3. The two commonest indications for acute PE are myasthenic crisis and in the preparation for thymectomy4. Chronic PE is a term to be used when the procedure is performed on a regular basis4 for a long interval5, and it is proposed for general-
PE is a therapeutic possibility in seropositive and seronegative forms of MG. Its efficiency is due to removal of proteins of autoimmune biological activity, mainly antibodies to acetylcholine receptor, leading to short-term improvement of neuromuscular junction transmission, muscular strength and motor performance. Usually, PE is combined with immunosuppressive treatment, such as prednisone, azathioprine or both, to avoid rebound effect and to maintain the improvement.

We analyzed our experience related to the indications, complications and outcome of PE in MG patients diagnosed and followed-up at the Neuromuscular Unit. Several aspects of the procedure itself were also retrospectively reviewed.

**METHOD**

We reviewed PE protocols of a consecutive series of patients from the Center of Hemotherapy and charts of MG patients attended at Unicamp Clinical Hospital. A casuistic of 26 patients was obtained. They were submitted to a total of 44 cycles and 171 sessions of PE, during 1993 to January 2002.

Clinical diagnosis of MG was complemented by laboratory exams, such as repetitive nerve stimulation tests, anti-acetylcholine receptor, anti-striational antibodies and CT images of mediastinum. Patients were classified according to the Osserman & Genkins (O & G) and MGFA (Myasthenia Gravis Foundation of America) scales expressing the clinical deficit before PE. Gender, age-onset of MG, level of serum antibodies, pathological results of the thymus and the disease status in follow-up were analyzed. Immediate outcome was assessed shortly after each PE cycle. Overall outcome was based in a follow-up period comprising the time between the last PE cycle up to January 2002. Patients were classified according to MGFA postintervention status.

Continuous-flow cell separators (Dideco Vivacell BT 798 CE/A, kit 480N400 or Fresenius AS 104, kit PL1) or discontinuous-flow separator (Haemonetics M CS 3 plus, kit 980/790) machines were employed. PE was scheduled preferably in an alternate-day intervals or three consecutive days plus two alternate-days sessions. A peripheral vein access was preferred whenever possible or a centrally placed Shiley’s catheter. Anticoagulation with citrate (ACD formula A), without heparin, was systematically used. Replacement of plasma removed during PE session was done with isotonic sterile saline, to make up one-half of the volume and with 4% purified human albumin to complete it. Since February 2000, 4% albumin was introduced earlier in the procedure and for two-thirds of the replacement volume. A careful monitoring of hemodynamic parameters was provided and complications during or following PE were rapidly recognized and reverted by rationale interventions of medical staff that assisted the procedure and the patient. Indications for PE, number of cycles and sessions, duration of each session, volume of plasma exchanged and patient tolerance to the procedure were systematically recorded. We assumed as mandatory to do microbiological culture of catheter’s extremity when it was removed.

**RESULTS**

Casuistic included 19 women and seven men; 19 whites and seven blacks. The mean age-onset of MG was 28 years, ranges 11 and 69. Clinical classification based on O & G was IIb (16 cases), III (8 cases) and IV (2 cases). Using MGFA scale cases were classified as IIIa (8 cases), IIIb (11 cases), IVb (2 cases) and V (5 cases). Eighteen patients were submitted to thymectomy and the histopathologic diagnosis thymus hyperplasia in eight and thymoma in two. In eight patients the gland was considered normal or exhibiting involution.

**DISCUSSION**

PE was firstly described as a therapeutic procedure for MG in 1976 by Pinching and Peters. During 1981-97 the disease was between the five most frequent indications for PE in Canada, but the second in 1997. A multicenter study from Taiwan showed that 34.9% of PE was indicated for MG patient. A restricted number of national publications about PE and MG was encountered. Seggia et al. from Rio de Janeiro analyzed costs and benefits of PE in the preparation of the therapy.
of patients for thymectomy.

The first MG patient submitted to PE at Unicamp Clinical Hospital was in 1993 and the present PE series includes about 17.8% of all MG patients followed-up at the Institution from 1982 to January 2002. The proportion of 2.7:1 for female:male and the demographic characteristics of the group represent the populations attended and the most severely diseased. Clinical manifestations of MG were recorded according to O & G scale as IIb (moderate generalized with bulbar signs) in 16 cases, III (acute fulminating) in eight cases, IV (late severe) in two cases. Regarding to MGFA scale, patients were classified as class IIIa (moderate weakness predominantly affect-

Table 1. Summary of data from the casuistic.

<table>
<thead>
<tr>
<th>Case</th>
<th>Gender</th>
<th>Race</th>
<th>MG age-onset (y)</th>
<th>O &amp; G</th>
<th>M GFA</th>
<th>Anti-AChR</th>
<th>Triational antibodies</th>
<th>Thymus gland</th>
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F, female; M, male; B, black; W, white; (y), years; For O & G = MGFA and abbreviations related with follow-up, see text; Anti-AChR, anti-acetylcholine receptor binding antibodies; reference values ≤ 0.02 nmol/L, *reference values < 0.8 nmol/L.; neg = negative; * death occurred 6 years and 3 months after thymectomy and 5 months after PE.
ing limb, axial muscle or both and lesser involvement of oropharyngeal muscles) in eight cases; IIb (deficit predominantly oropharyngeal and/or respiratory plus limb and/or axial muscles lesser involved) in 11 cases; IVb (severe weakness predominantly affecting oropharyngeal and/or respiratory muscles, may also have lesser or equal deficit of limb, axial muscles or both) in two and class V (intubated, with or without mechanical ventilation) in five cases. The least severe grade of the disease for which we indicated PE was IIb according to O & G, corresponding to IIIa in the MGFA scale. PE was indicated due to myasthenic crisis in seven cases, 26.9 % of the casuistic. Werneck et al.20 used PE as specific treatment in 16.6 % of 24 cases of these potentially fatal condition.

In case 6 PE was performed four days previous to thymectomy for preparing the patient to surgery, as suggested by others7,12,13. The patient had difficulty in the maintenance of motor strength while lowering prednisone. As expected postoperative result was uneventful. Dias-Tosta and Fernandes14 reported eight patients submitted to PE: five indicated as prethymectomy in cases with restricted vital capacity and in three cases the procedure was performed after surgery because worsening of motor power.

In 18 cases PE was indicated because severe motor deficit, especially bulbar dysfunction or due to exacerbation of deficit induced by corticosteroid. This drug is the first choice in the therapy of MG, regarding the autoimmune aspects of the disease, but half of the patients may worsen, requiring careful monitoring1.

Cases 2 and 24 were submitted to PE also because other therapies failed to achieve the necessary sustained motor performance for daily life activities. They had 6 and 5 cycles of PE respectively, in a monthly schedule of two consecutive days sessions. Chronic PE was proposed by Kornfeld et al.6 as effective therapy in cases of generalized MG refractory to other treatments. Rodnitzky and Bosch2 described two cases of intermittent PE therapy prescribed up to five years without significant side effects.

Korach et al.21 observed that immediate complications of PE decreased by half in the last 15 years according to the French registry. Anticoagulation with sodium citrate solution was responsible for 3% of side effects in all PE procedures22, like perioral tingling, trembling, dizziness and hypotension23,24. Hypocalcemia resulted in mild paresthesias and tremor in seven of our patients. Vasovagal attack with concomitant hypotension, true hypovolemia or fluid overload may also be complications of PE25. Hypotension occurred in seven of our 26 patients and was reversed by fluid replacement. In a group of 144 sessions of PE, Wendell Neto et al.19 encountered 10.4 % of paresthesias, 2 % of hypotension and 10.4 % of allergic reactions. Seggia et al.17 also presented a list of PE side effects in their patients, all easily managed.

Placement of the central catheter can be the cause of major complications associated with PE, such as pneumothorax, thrombosis or infection24,25. Microbiological culture of catheter’s extremity was always negative in our patients. In our series there was no death directly related to PE. In case 13, the patient was a chronic ventilator dependent with diaphragmatic paralysis. She had a prolonged hospitalization, evolving to death from sepsis that occurred five months after PE. Kiprov et al.24 found a mortality rate of 0.006% from two large mobile apheresis services. In a survey of seven years PE in Mexico, the mortality rate was 0.2%26.

In conclusion, acute PE was a rational treatment for patients with myasthenic crisis and in preparation for thymectomy. It had a favorable short-term impact on severe weakness and exacerbation of symptoms. PE was used in association with prednisone or other immunosuppressor while waiting for further stable improvement or disease remission. On a chronic intermittent basis, PE was indicated for patients who had previously failed to respond to other therapies. In our cases immediate improvement in motor performance was detected, either by a reduction of deficit or a diminution of daily doses of cholinesterase inhibitors and of immunosuppressive drugs.

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