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Therapeutic plasma exchange in neuroimmune diseases. Rehabilitation in myasthenia gravis patients treated with apheresis procedures

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Abstract

Therapeutic plasma exchange (TPE) is an extracorporeal blood purification technique which removes large molecular weight particles, like autoantibodies, from plasma. Double filtration plasmapheresis (DFPP) is a newer technique in which plasma is not entirely removed, only the antibodies, using special filters. Myasthenia gravis (MG) is a well-known autoimmune disease characterized by antibodies against postsynaptic nicotinic acetylcholine receptors and fluctuating weakness, sometimes life-threatening. TPE is a therapeutic modality well established in MG with a positive recommendation based on strong consensus of class III evidence and in the category I of American society for apheresis. There are no adequate randomized control trial, but many cases report short-term benefit from plasma exchange in MG especially MGC. We analyzed the cases of neuroimmune disorders that were presented to our Emergency Care Unit between 2012-2020 and we concluded that good acceptance of procedure (TPE/DFPP) was observed in 72% of patients. TPE is cost-effective rapid therapy for myasthenic crisis and progressive myasthenia gravis. It reduces ICU stays and improves outcome.All in all recent studies show that the combination of rehabilitation and other forms of treatment, appropriately selected activities contribute to alleviating the symptoms of the disease, improving physical fitness, increasing muscle strength, and thus improving the quality of life.

Keywords: *therapeutic plasma exchange, plasmapheresis, neuroimmune disorders,rehabilitation,*

Introduction

Rehabilitation is defined as “a set of measures that assist individuals who experience disability to achieve and maintain optimal physical, sensory, intellectual, psychological and social functioning in interaction with their environment” (World Health Organization. World Report on Disability. Geneva, Switzerland: WHO; 2011).

Furthermore, an efective rehabilitation program can minimize secondary medical comorbidities, prevent or limit physical deformities, and allow the patient to integrate into society.Myasthenia gravis (MG) is a well-known autoimmune disease characterized by antibodies against postsynaptic nicotinic acetylcholine receptors and fluctuating weakness, sometimes life-threatening. MG has annual incidence of approximately 30 new cases per million, approximately 15–20% of these patients will go into myasthenia gravis crisis (MGC) and 3–8% of all patients who go into MGC will die from this condition (1).Therapeutic Plasma Exchange (TPE) is accepted by the American Society for Apheresis as first line treatment for some severe neuroimmune disorders. TPE is a therapeutic modality well established in MG with a positive recommendation based on strong consensus of class III evidence and in the category I of American society for apheresis. It can be as well used for other pathologies being very often used for patients that suffer fromGuillanBarre Syndrome, Myasthenia Gravis as it will behighlighted further and sometimes Multiple Sclerosis (1). The exact mechanism by which apheresis treatment works in multiple sclerosis is actually not fully understood. MS patients may benefit by the immediate removal of plasma antibodies, immune complexes and cytokines. Besides effects on humoral immune system, experimental data suggest a reduction of circulating autoantigens and regulatory proteins and induction of a higher relative quantity of Treg to Th17 cells (2). Th17 is known to transfer immune and inflammatory processes through the BBB using different mechanisms: penetrating the BBB, inducing neuronal death and recruiting other CD4+ lymphocytes, thus promoting further CNS inflammation, whuch can lead to disease worsening and exacerbations. This made clear that Th17 cells are implicated in early MS pathologyand that plasmapheresis should be taken into consideration as an effective treatment (2).

2.Matherials and methods.Results.

Firstly, we would like to present the experience of our centre in therapeutic plasma exchange. We started using

therapeutic plasma exchange (TPE) and double filtration plasmapheresis (DFPP) in 2012 (Fig 1).

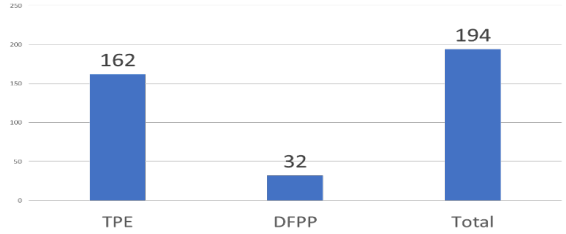

Figure 1 –number of TPE and DFPP since 2012

Since then 68 pacients benefited from this procedures. Out of them 42 were patients that suffered from neuroimmune diseases, 10 being diagnosed with Miyasthenia Gravis (Fig 2).

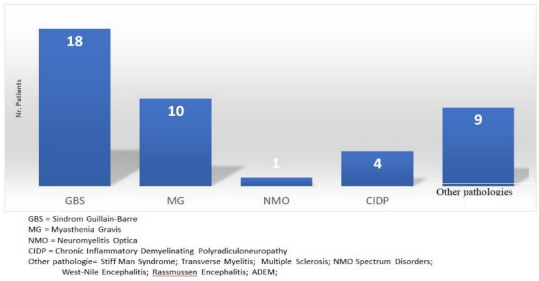

Figure 2 – pacients with neuroimmune pathologies that underwent TPE/DFPP

All the patients that were treated with one of these procedures were admitted in ICU until the procedures were over. The right or left internal jugular vein was catheterized with a 20 F double lumen catheter, this procedure being performed under local anesthesia, with an aseptic technique. X-ray control is always performed to assure proper position of the catheter. For both techniques (TPE, DFFP) we used the HF440 machine (Infomed SA, Geneva-Switzerland). Cascadefiltration is a 2 steps process during which plasma is first extracted from the blood and then circulated through a second filter, the plasmafractionator.Having a membrane pore size approximately 10 folds smaller than a plasmafilter, the plasma fractionator retains larger molecules such as IgG, LDL-cholesterol and viruses.

The mean age of the pacients treated with TPE was between 50-60 years (Fig 3). The adverse reactions (hypocalcemia, hyponatremia, hypokalemia, hypotension, infections, allergic dermatitis)described in the group of patients subjected to these procedures, similar to those described in the literature, were transient, completely reversible and did not require discontinuation of the procedure in the study group.The adverse reactions usually appear after the administration of albumin as replacement fluid. For example this case of GBS when after administration of first dose of albumin the patient experienced arrhythmias, marked dyspnea, hypotension (blood pressure 50/30mmHg), bradycardia (heart rate 40 beats/min), symptomatology that partially remitted under cortisone therapy and adrenaline (3). Hypotension is a rare adverse reaction, the most common side effect to TPE being hypocalcemia that appears because of chelation of calcium by sodium citrate, used as an anticoagulant both during the procedure and in thawed fresh frozen plasma often used for replacement (4). However, we would like to highlight that most of the patients (72%) that underwent these procedures got ameliorated (Fig 4).

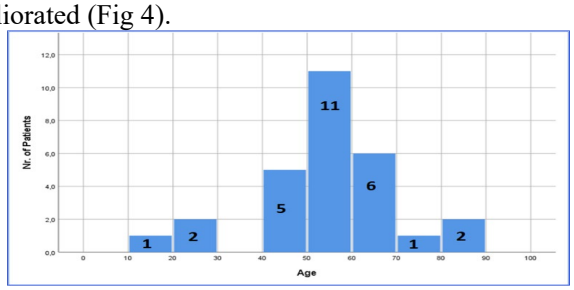

Figure 3 – median age of the patients that underwent therapeutic plasma exchange/double filtration plasmapheresis

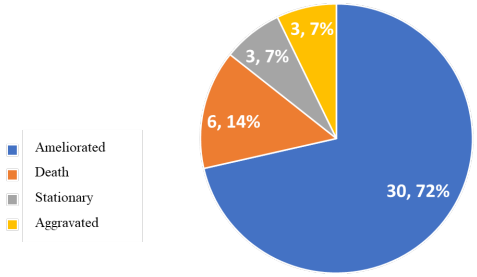

Figure 4 – clinical evolution of the patients after TPE and DFPP

Deaths (14% of patients) were not due to the procedure itself, being caused by sepsis / bronchopneumonia (Fig 5).

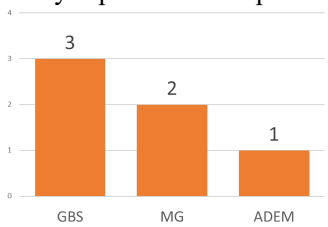

Figure 5 – number of deaths appeared after the procedures

3. Case Report

Plasma exchange procedures (TPE and DFPP) used by an experienced team in intensive care clinics are a safe method of treatment in severe neuroimmune diseases, therefore we would like to present the case of a 44 years old patient, known with Myasthenia GravisOssermannIIIa, that was admitted to our intensive care unit for deglutition problems, extreme fatigability, breathing difficulties and dysphonia. The symptoms started 5 days prior admission into the hospital, secondary to a pulmonar infection for which she underwent antibiotic treatment.

Clinical and Neurological exam at admission revealed: very influenced state, blood pressure - 120/70 mmHg and 80 beats/minute the heart rate, she was intubated and mecanical ventilated. She had no fever and no other abnormalities at the general examination.

It is well known that therapeutic plasma exchange or IV imunoglobulins are life-saving in patients with myasthenic attacks.

Patient underwent TPE (Therapeutic Plasma Exchange) with apheretic devices on alternate days using 4% human serum albumin (HSA) and normal saline (NS) as replacement fluid. One to one-and-a-half plasma volumes were exchanged in each session with a total of 11,832 ml of patient plasma over a period of 10 days. The patient had significant improvement in her respiratory profile and was extubated. In addition, there was improvement in the overall muscle power and she was able to move without support.

We would like to emphasize the importance of plasma exchange in patients with autoimmune pathologies and the major significance of rehabilitation right after the procedure. The present case is an example of myasthenia gravis with repeated crisis attacks despite being on regular maintenance immunosuppressive therapy for the last 14 months; and, significant improvement has been seen after multiple sessions of TPE.

4. Discussions

In general, refractory cases of myasthenia gravis respond to aggressive immunosuppression and other immunosuppressive therapy including rituximab.The treatment efficacy of IVIg and TPE has been found to be equally effective with the former being preferred due to the ease of administration.

All in all, after the procedures are over, it is very important the rehabilitation of these patients. The research shows that the combination of rehabilitation and other forms of treatment, appropriately selected activities contribute to alleviating the symptoms of the disease, improving physical fitness, increasing muscle strength, and thus improving the quality of life.

Physical Training

In the prospective pilot study by Westerberg et al. (2017) (5), 10MG patients with a mild

form of the disease performed supervised aerobic and resistance training twice weekly for 12 weeks.

Physical exercise was well tolerated, and the Myasthenia Gravis Composite (MGC) score was unchanged.

Physical performance-based measures improved while muscle enzymes remained normal.

In their 2018 study, Westerberg et al. (6) evaluated functional skeletal muscle parameters in11 MG patients, before and after conducting a 12-week supervised physical therapy regimen of aerobic and resistance strength training. After the training program, physical performance-based measures improved as well as the clinical MG composite score.

The aim of the study by Farrugia et al. (2018) (7) was to investigate whether a combinationof physical and psychological therapy would help address symptoms of fatigue in ten MG patients, who have stable disease but residual problematic fatigue. There was a significant improvement in the visual analogue fatigue scale (VAFS) at the end of the program. No clear improvement was noted in the other scales. Three months later, all fatigue scores declined to baseline.

Respiratory Training

Weakening of muscles including respiratory muscles may lead to respiratory failure. Therefore, it is important to introduce the improvement of breathing exercises in the program. In available publications, the authors suggests various forms of rehabilitation - inspiratory and expiratory muscle training, breathing membrane training or endurance training. All forms of rehabilitation used bring beneficial health effects for patients, which confirms that respiratory muscle training is an important and effective element of therapy (8, 9, 10).

Aslan et al. (2014) (11) carried out an RCT investigating the efects of respiratory muscle training performed by inspiratory and expiratory threshold loading on pulmonary functions in 26 patients with slowly progressive neuromuscular disease, including MG. Maximal inspiratory and expiratory pressures and snff nasal inspiratory pressure were improved in the experimental group when compared with the sham group ($p < 0.05$). However, there was no improvement in spirometric measurements when groups were compared ($p > 0.05$).

The prospective case-control study by Freitag et al. (2018) (12) investigated the efects of asixteen-weeks respiratory muscle endurance training (RMET) on MGpatients and compared the results with a control group. Eighteen patients with mild to moderate MG participated as the training group, and six patients served as controls. A modulation in the breathing pattern at rest with prolonged expiration was observed in the training group. In addition, the training group reported subjective improvements in MG symptoms, respiratory symptoms, and physical fitness. No significant changes were observed in the control group.

Balance Training

An important part of the rehabilitation process in myasthenia is balance training. Patients with MG lead a more sedentary lifestyle compared to healthy people. This affects, among other things, the reduction of bone density and, consequently, can lead to falls and fractures. During exercise, there are various physiological effects - increased skeletal muscle mass, increased number of mitochondria, which in effect improves the efficiency of neuromuscular transmission (13).

The prospective study byWong et al. (2014) (14) aimed to determine if a 16 session workstation

intervention consisting of balance strategy training (BST) could improve functional ability and balance in a group of seven individuals with MG. The quantitative myasthenia gravis score (QMG), timed up and go with cognitive task (TUG-cognitive), and foam with eyes closed (foam EC) achieved clinically significant improvements (>15%).

Cardiac Rehabilitation in Myasthenia Gravis.

Patients with MG are frequently discouraged from enrolling in cardiac rehabilitation by their healthcare providers or denied care at rehabilitation centers not equipped for care of such patients. Our report shows that aerobic and resistance exercise may be safe and effective for MG patients in a cardiac rehabilitation setting. Careful individualized

planning; close monitoring and frequent reassessments are warranted to ensure that the benefits of training outweighing the risks associated with exercise in MG patients (15).

The main finding of this systematic review is that there is a critical lack of high-quality evidencefor the efectiveness of various rehabilitation modalities for people with MG; although a spectrumof interventions is proposed, the evidence for many of these are limited due to a paucity of robust, methodologically strong studies.

The rehabilitative approaches most frequently evaluated in the selected studies were physical and respiratory training.

Physical training, which includes aerobic, strength, and progressive resistance exercises, has proven to be an e_cient strategy to improve functional outcomes (mobility, muscle strength, aerobic capacity), fatigue, physical performance, and quality of life in people with MG. The greatest benefits of physical training have been achieved in patients with a mild to moderate MG and practiced under a limited training intensity (16).

It has also been stated that general recommendations concerning physical exercise could be applied safely to patients with a well-regulated MG (16). A study even showed that long-term physical activity could reduce the autoimmune response (5). Furthermore, there was general agreement among selected studies that physical training is well tolerated by patients with MG and that the pathology does not deteriorate with physical activity (5, 10).

5. Conclusions

Clinically stable MG patients, just like healthy individuals, should be able to reap the benefits of physical exercise and we suggest that a reasonable program to begin with is to follow the minimum recommended international guidelines on exercise for healthy adults, i.e., at least 150 min of moderate intensity exercise a week.

As MG by its nature can involve fluctuations in symptoms dependent or independent of physical exercise, patients should always contact their physician if experiencing sustained worsening of symptoms, to receive supportive advice on further management.

TPE proved its efficacy as an emergency life-saving procedure in myasthenia crisis and is also useful as long-term maintenance therapy in patients refractory to IVIg and other immunosuppressive therapy due to its immunomodulatory effects.

Conflict of interest

No conflict of interest for any of the authors regarding this paper.

Informed consent

An informed consent was obtained from the patients (or the tutor of the patients) included in this article.

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