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Improvement of quality of life after therapeutic plasma exchange in patients with myasthenic crisis

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ABSTRACT

Introduction: We sought to evaluate quality of life patients with myasthenic crisis before and after therapeutic plasma exchange.

Materials and methods: In our study we conducted an assessment of the quality of life with the use of the questionnaire SF-36, when executed eleven therapeutic plasma exchange. The assessment was made on baseline and after 4 weeks. We also did neurological clinical evaluation before and after TPE.

Results: Patients in the study showed significant improvement in quality of life after performed therapeutic plasma exchange. The changes were observed in physical functioning, which confirmed the results of the statistical significance of $p < 0.05$. In the analysis, the assessment of mental functioning not obtained the results of statistical significance, but the results also showed improvement in self-assessment. We observed high correlation between general health and physical mental functioning, between the role limitations due to physical health problems and role limitations due to emotional problems, and general health perception and bodily pain.

Conclusions: Therapeutic plasma exchange significantly improves the quality of life of patients with myasthenia gravis during the crisis.

1. Introduction

Myasthenia gravis (MG) is an acquired autoimmune disease with pathomechanism based on production of antibodies directed against acetylocholine receptors (anti-AchR) of the postsynaptic membrane of the neuromuscular junction. The epidemiological examinations showed that the disease occurs with frequency of 10–15 persons per 100,000 population. The main symptom of myasthenia is progressive muscle fatigability, the typical of which are: apokamnosis symptoms of limbs muscles and mimetic muscles, diplopy, eyelids drooping, ''snarling'' smile the so-called Gioconda's syndrome, difficulty chewing, dysphagia, dysarthria [1]. In conformity with

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Osserman's classification two basic types of the disease can be distinguished: ocular (type 1) and generalized (type 2). The criteria for classification of patients into particular types of myasthenia are exclusively clinical symptoms [2,3].

The diagnostics of myasthenia is based on marking the level of antibodies anti-AChR, which occur at 85% patients. The remaining 15% described as seronegative may have other types of antibodies, such as against muscle-specific tyrosine kinase (anty-MuSK) or antititin antibodies [4–6]

In case of rapid increase of the symptoms and acute course of the disease leading to respiratory inefficiency talk about the myasthenic crisis. It is estimated that every fifth patient has at least one myasthenic crisis in a lifetime and, if the disease is accompanied by thymoma, the risk increases to 50% [7]. The myasthenic crisis usually occurs at patients with generalized type of disease, the symptoms of respiratory inefficiency are accompanied by significant fatiguing of muscles, swallowing disorders, bulbar palsy [8].

The standard procedure in case of the occurrence of the myasthenic crisis is treatment of the patient in an intensive care ward. It is important to implement the therapy (plasmapheresis or intravenous supply of immunoglobulins) as soon as possible, which will allow the shortening of application of mechanical ventilation and limitation of the risk of complications [9].

The patients with diagnosed myasthenia are characterized by a significant variability of the course of their disease. Some of them complain on numerous clinical symptoms, which in a small or a bigger extent make everyday life difficult. The patients understand the concept of health as a functional condition and a quality of life with the disease. The evaluation of the quality of life has in recent years become an important element of everyday medical practice, since the purposes of modern medicine are both prolonging patients' lives as well as improvement and approximating the quality of life to the condition before the disease. In our research we mainly use the definition of the quality of life condition by the health condition (health related quality of life – HRQOL). This value is estimated subjectively by a patient and involves the comparison of the present health condition with the expected condition using respectively general questionnaires, specific and mixed questionnaires [10].

The aim of our study was to evaluate for the first time in our Polish population patients with myasthenic crisis the quality of life before and after therapeutic plasma exchange.

2. Materials and methods

2.1. Patient population

Into the prospective study eleven cases diagnosed with myasthenia during the myasthenic crisis who had been qualified for TPE were enrolled. Only conscious, cooperating, able to fulfilling the questionnaires subjects were included into the study. Demographic patients' characteristics were presented in Table 1. TPE were conducted in patients submitted to therapeutic plasma exchange during years 2012–2015 in the Ward of Anaesthesiology and Intensive Therapy. The work described in this article has been carried out in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans Nr KNW/0022/KB1/68/15; uniform requirements for manuscripts submitted to biomedical journals.

Table 1 – Demographic and clinical characteristics of patients enrolled into the study.

TPE (*n*)	11
Average age (years)	59 (51–71)
Gender (%)	75 (female) 25 (male)
The mean duration of illness (years)	14 (3–32)
Tymectomia (%)	80 (%)
Main neurological symptoms before TPE (%)	Apokamnosis symptoms of limbs muscles and mimetic muscles (100%) Diplopy (81%) Eyelids drooping (75%) Difficulty chewing (63%) Dysphagia (75%) Dysarthria (81%) Dyspnoea (81%)
Electrical activity in repetitive nerve stimulation (%)	Positive (100%)
Antibodies against AchR before TPE (nmol/l) [range/mean]	15.8–1300 (253.17)
Antibodies against AchR after TPE (nmol/l) [range/mean]	39.4–320 nmo/l/179.7
Treatment (%)	Anticholinesterase drugs (100%) Prednisone (27%) Azathioprine (18%)
CRP (mg/l) [range/mean]	0.48–20.92/4.24

TPE – therapeutic plasma exchange, CRP – C-reactive protein.

2.2. Therapeutic plasma exchange

TPE (plasmapheresis) is a method of blood purification allowing to remove inflammatory mediators and antibodies by using extracorporeal circuit. The procedure is used in a variety of conditions, including autoimmune diseases like myasthenia (indication IA during American Society for Apheresis) [11]. TPE is an invasive procedure, but when performed by properly trained and qualified staff, it is relatively safe [12–14]. Life-threatening episodes like shock (anaphylactic or septic), hypotension requiring vasopressor drugs or bleeding are rare [12–14]. The most frequent, but not very severe complications are urticaria, pruritus, hypocalcaemia and mild hypovolemia. Adverse effects are associated more commonly with the administration of fresh-frozen plasma (FFP) used as a replacement solution compared to human albumin solutions.

Patients with diagnosed myasthenia were qualified to TPE by neurologist, based on clinical state and the level of acetylcholine receptor binding antibodies. In Poland TPE is performed in Intensive Care Units, regarding patient's clinical state, often requiring respiratory or circulatory support. Because of many different indications (plasmaphereses are used in treatment of about 150 diseases) and various equipment available, one standard TPE protocol does not exist. We developed our own TPE protocol based on previous

Table 2 – MGFA clinical classification.

Class I	Any ocular muscle weakness; may have weakness of eye closure. All other muscle strength is normal.
Class II a	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. Predominantly affecting limb, axial muscles, or both.
Class II b	Mild weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. Predominantly affecting oropharyngeal, respiratory muscles, or both.
Class III a	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. Predominantly affecting limb, axial muscles, or both.
Class III b	Moderate weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. Predominantly affecting oropharyngeal, respiratory muscles, or both.
Class IV a	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. Predominantly affecting limb, axial muscles, or both.
Class IV b	Severe weakness affecting muscles other than ocular muscles; may also have ocular muscle weakness of any severity. Predominantly affecting oropharyngeal, respiratory muscles, or both.
Class V	Defined as intubation, with or without mechanical ventilation, except when employed during routine postoperative management. The use of a feeding tube without intubation places the patient in class IVb.

publications and experiences [12–15]. In our ICU membrane filtration types of plasmapheresis is performed with standard heparine anticoagulation, using TPE 2000 filter for Prismaflex eXeed system (Gambro-Baxter). The central venous catheter 12 Fr is inserted with ultrasound guidance using Seldiger technique, usually via right internal jugular vein. Standard biochemistry, morphology, coagulation, electrolytes and blood arterial gases are assessed in every patient. Before starting the procedure, patients are given 500–1000 ml of crystalloid fluid with calcium. During one session the exchanged plasma volume is 50 ml $h^{-1}$with median 3000 ml. It is about 1–1.2 of estimated plasma volume (EPV) according to Kaplan rule: EPV = [0.065 × weight (kg) × (1 − Ht)]. Blood flow rate was set at 2 times body weight, but did not exceed 200 ml h^{-1}. As a replacement fluid we used PrismaSol 4 or Phoxilium (containing 1.2 mmol phosphate) dialysate solution with mean flow rate of 700 ml h^{-1}. Additionally, every patient received 450–500 ml of 20% human albumin solution (Flexbumin, Baxter) immediately via peripheral vein access. Anticoagulation is maintained with heparin infusion 800–1000 IU h^{-1}, without additional boluses. Fluid removal from the patient depends on haemodynamic stability. Median duration of session was 5 h. At the end of each session, one unit of FFP was administered, as well as vitamins and calcium. Sessions were repeated every day or every other day. After 3–4 sessions significant clinical improvement was observed. In our group no treatment was discontinued due to a complication or clotting in circuit. In 2 cases mild hypotonia was observed, in 2 cases transient dysrhythmias occurred due to electrolyte imbalance. No serious adverse events were observed [12–15].

2.3. *Neurological clinical evaluation*

We used standard classification system for the neurological clinical evaluation before and after TPE. Myasthenia Gravis Foundation of America clinical classification (MGFA) may be used to define prognosis and possible response to treatment. Class I is mild in nature, Classes II, III and IV may be further subdivided into category 'a', which primarily impacts the limbs, or 'b', which primarily affects the respiratory muscles or those of the tongue or mouth. Class V is the most severe form requiring intubation [16]. Table 2 showed complete MGFA Clinical Classification.

2.4. *Quality of life evaluation*

Before and after TPE procedure the patients were asked to fill a validated Polish language version SF-36 form created by Professor J. Tylka on the basis of original English language version The Short Form 36 Health Survey [17,18]. It consists of thirty six questions assessing: PF – physical functioning, RLP – role limitations due to physical health problems, BP – bodily pain, SF – social functioning, GMH – general mental health, RLE – role limitations due to emotional problems, VT – vitality, GHP – general health perception. An additional parameter assessed in the form is a change in the health condition over time (a recent year). This index was not included in the above components of SF-36. Categories are grouped in two scales: physical (PCS – Physical Component Scores) and mental (MCS – Mental Component Summary). To scale PCS included in categories: PF, RPL, BP, GHP, and to the scale of MCS – Categories: RLE, SF, GMH, VT.

The answers to each question are evaluated according to a point scale and then converted into particular numeric values for specific indices. The results are presented separately for each of the eight indices and in total for all components of form SF-36 as HRQOL – health quality of life index. The maximum scores to evaluate the quality of life in questionnaire SF 36 is 171 points, where the physical aspect of life is maximum 103 points, and psychical 68 points.

The overall assessment serves to determine the quality of life where in conformity with the Polish interpretation it was assumed that the highest point value means the lowest degree in evaluation of the quality of life and the lowest value – the highest quality of life level.

2.5. *Statistical analysis*

The study results were conducted on the grounds of statistical analysis for quantitative parameters, for which basic descriptive statistics were determined: average, standard deviation, median, extreme values, variations. The force and direction of interdependence of the score in SF-36 form before and after the TPE was determined using Spearman' correlation coefficient *r*. The statistical analysis was conducted using programmes STATISTICA v. 12 PL and EXCEL.

3. Results

Results from our study obtained from the SF-36 form indicate that the patients after TPE notice improvement the quality of life in all examined components in the group of patients qualified for the therapeutic plasma exchange during the course of aggraviation of a myashtenia. The overall coefficient of the SF-36 amounted on average 119.81 and 83.90 points ($p < 0.05$) before and after the treatment, respectively.

Neurological clinical evaluation also showed positive changes in all patinets. MG patients before TPE were categorized in range IIIa–V according to the MGFA Clinical Classification. MG cases after TPE were categorized in range I–IIb according to the MGFA. Table 3 presents a summary of MGFA Clinical Classification in patients before and after TPE.

Physical Component Scores – PCS, which consists of physical functioning (PF), role limitations due to physical health problems (RLP), bodily pain (BP) and general health perception (GHP) showed a statistically significant correlation ($p < 0.05$) as regards the self-assessment of the quality of life before and after the therapeutic plasma exchange.

The compared results of Mental Component Scores – MCS, consisting of: social functioning (SF), role limitations due to emotional problems (RLE), general mental health (GMH) and vitality (VT) do not significantly differ as regards the self-assessment of the quality of life in this area ($p > 0.05$). The health condition changes over time not included in the assessment of physical and mental health did not show significant differences ($p > 0.05$) among the examined patients. Table 4 presents a summary of SF-36 form results in particular categories for the examined patients.

The subjective improvement quality of life is confirmed by results from clinical examination. The patients with slight disease severity (MGFA class IIIa and IIIb) had a lower PCS, that mean higer quality of physical functioning after TPE. MG patients of the MGFA Class IVa, IVb and V achieved a higher rate of PCS. Results show significant differences ($p < 0.05$). The MGFA Class changes compared in the assessment of mental health did not show significant differences ($p > 0.05$) among the examined patients.

Table 3 – The summary of MGFA Clinical Classification in patients before and after TPE.

Patient no.	MGFA Class before TPE	MGFA Class after TPE
1	III a	II a
2	IV b	II a
3	IV a	I
4	III a	I
5	IV b	I
6	IV a	II a
7	IV b	II b
8	III b	II b
9	III a	II a
10	V	II b
11	IV b	II a

Differences in quality of life in particular domains are not homogenous. The patients notice the biggest improvement mainly in physical condition aspect. In the scope of physical limitations quality of life the patients who had undergone TPE obtained lower scores in comparison to self-assessment during the period of aggraviation of myasthenia, i.e. before the treatments. The patients scored respectively 56.54 vs 77.27 points. The lower score means higher quality of life. The most significant differences were noted in categories: physical functioning, general health perception and bodily pain. The differences in these categories were statistically significant ($p < 0.05$) and amounted respectively – for PF 39.0 vs 28.63, for GHP 14.72 vs 10.72 and for BP 4.5 vs 3.5 points.

The quality of life assessment in the mental sphere did not show any statistically significant differences. The patients before TPE scored 39.27 points, and after therapeutic plasma exchange – 26.45 points. The biggest improvement was noticed in category role limitations due to emotional problems 10.5 vs 5.5 and vitality 14.1 vs 8.72 poitns (Fig. 1).

Spearman correlation analysis between the dimensions of health showed a high correlation between general health and physical mental functioning ($r = 0.72$), between the role limitations due to physical health problems and role limitations due to emotional problems ($r = 0.62$), and general health perception and bodily pain ($r = 0.74$).

Table 4 – The SF-36 – summary of results of patients before and after TPE.

	Before TPE			After TPE			
	Mean	Median	SD	Mean	Median	SD	p
Physical functioning (PF)[a]	39	44	13.34	28.63	34	11.21	<0.05
Role limitations due to physical healths problems (RLP)[a]	19.09	20	2.02	16.63	15	4.52	NS
Bodily pain (BP)[a]	4.45	5	1.69	3.54	4	1.21	<0.05
General health perception (GHP)[a]	14.72	15	4.84	10.72	11	2.45	<0.05
Social functioning (SF)[a]	5.09	6	1.76	2.81	3	1.54	NS
General mental health (GMH)[a]	9.64	8	5.08	9.45	8	6.04	NS
Role limitations due to emotional problems (RLE)[a]	10.45	15	6.11	5.45	5	4.16	NS
Vitality (VT)[a]	14.09	16	4.78	8.72	9	3.35	NS
Health Change[a]	3.27	4	1.42	0.9	1	0.94	NS

TPE – therapeutic plasma exchange.
[a] Points.

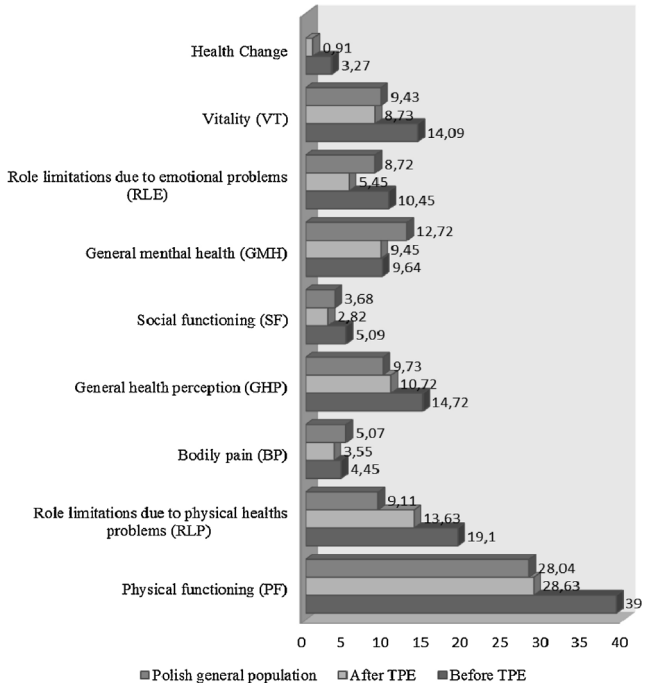

Fig. 1 – Quality of life (SF-36) before TPE, after TPE and general Polish population – average results obtained in each category (points) [28].

4. Discussion

Our study proved improvement in the quality of life scores in patients with myasthenia after therapeutic plasma exchange. The increased interest in quality of life depends on the health in the context of existing chronic disease is now one of the most important trends in research. Quality of life allows to assess the influence by illness and treatment on physical, mental and social development of the patient and can be helpful in building a comprehensive therapeutic strategy, relating not only to improve the physical aspect. In patients with myasthenia, particularly because it is a chronic disease which affects significantly the patients' quality of life depending on the intensity of neurological symptoms. If a myasthenic crisis occurs, the patients' functioning rapidly deteriorates and thus the quality of life level decreases. The questionnaire SF-36 questionnaire as a general, was chosen for this study because of its complexity and the high standard of reliability and credibility. Analysis of results also showed that the MGFA Clinical Classification is corresponding with subjective quality of life patients with myasthenia. It becomes a important predictor of clinical results after TPE treatment. The MGFA class is actually used in evaluation of neurological changes after different treatment of myasthenia, in patient with thymoma and after surgical intervention or as prognostic factor. It gives possibility to objectively clinical evaluation [19].

Our assumptions before study were that the scores in the group after the treatment would be significantly better, especially in the aspect of physical functioning. We received statistical results $p < 0.05$ what confirmed our assumptions. Significant improvement after TPE was also noticed in the mental functioning, but no statistical results were obtained.

In conformity with current guidelines the TPE show efficiency comparable to immunoglobulins 'treatment in the course of mysthenic crisis [20]. The so-far conducted research did not prove significant advantage of one of these methods, however, the improvement effect is usually faster achieved after TPE application. The equivalence of both above mentioned treatments provides a free possibility of choosing a procedure and adjusting a proper scheme of procedures for a specific patient [21,22].

So far in the literature there were scarce works concerning the quality of life patients with myasthenia. Barnett et al. in their study compared the improvement in the quality of life (HRQOL) after immunomodulation. They assessed the questionnaire MG-HRQOL-60 after IVIG and TPE in 62 patients and then analyzed the change in the HRQOL scores from baseline to day 14 in both treatment groups. Results showed the scores in both HRQOL scales decreased at day 14 in the IVIG and TPE groups, without significant difference between groups. Changes observed in questionnaire MG-HRQOL-60 presents that IVIG and TPE are comparable in the treatment of patients with myasthenia [23]. In our study we also observed improvement in quality of life after TOP. Most significantly changes were shown in physical functioning, especially in physical functioning, general health perception and bodily pain. Results were statistically significant ($p < 0.05$).

Study conducted by Chen et al. appraised the effects of improvement in muscle strength after TPE on both quality of life and psychological status of MG patients. Psychosocial tests showed significant pre- and posttherapy differences in illness identity and disability. Patients especially were achieving immediate improvement of myasthenic symptoms but emotional status and HRQOL did not differ significantly after intervention [24]. Our observations were similarly. Mental functioning has been less improvement than the physical aspect, and the results did not reach statistical significance.

Boldingh et al. in their work assessed the quality of life patients in Scandinavian countries diagnosed with myasthenia compared to general population. Used in this study SF-36 form assessed the recent four weeks from patients' lives. The patients were divided depending on clinical symptoms of the disease, disease remission period, gender, applied treatment, antibodies presence and thymoma. No statistically significant differences between HRQOL at patients with diagnosed myasthenia versus general population were found. Nevertheless, it was observed that certain conditionings, such as female gender, general fatigability or usage of secondary non-steroid immunosuppressive were risk factors to reduced HRQOL [25].

The research conducted by Padua et al. in Italian population was involved the evaluation of the correlation of neurological symptoms and repetitive nerve stimulation patients with myasthenia. Results were compared to HRQOL outcomes based on SF-36 form both patients with MG and health population. All domains were reduced in patients with myasthenia (lower HRQOL) compared to normative Italian population [26]. In reference to the above two studies, in our study we made a summary of the results obtained in patients with myasthenia before and after TPE with respect to the norm of Polish population in HRQOL (based on SF-36). The results are

contained in Fig. 1. Evaluation of the quality of life of patients diagnosed with myasthenia showed lower HRQOL compared to the general population, without statistically significant differences ($p < 0.05$).

Kilkantrakorn et al. reported that mental functioning results showed the lowest scores (lower HRQOL) while other components were in average or high range. Better physical functioning were observed in patients with ocular and mild generalized myasthenia. Immunosuppressive treatment was not associated with low quality of life. Females had lower scores of HRQOL in MG patients using SF-36 form [27]. Our results indicate similar conclusions. Patients with mild symptoms of myasthenia had a better result in evaluation of quality of life. Mental functioning showed lower improvement in HRQOL after TPE than physical aspect of life.

Amount of studies conducted so far in assessing the quality of life of patients with MG treated IVIG or TPE is still low. However, for patients changes that improve their physical, psychological and social aspects of life are very important. Myasthenia is a chronic disease with which patients have to struggle for life. Systematical evaluation for patients' illness perceptions and emotional problems are warranted and related strategies should be taken for long-term stabilization of psychosocial function.

5. Conclusions

In conformity with the our obtained results the patients treated with TPE together with disappearance of clinical symptoms observed a significant improvement in their quality of life. Significant differences regarded the physical functioning aspect. It may be said that nowadays the patients' quality of life is also an element of the treatment efficiency. A possibility to have family and professional life, do every day activities without obstacles is an important indicator in all assessments. We are aware about the limitation of our study what is the number of patients qualified for TPE. Further studies concerning the assessment of the quality of life among patients with myasthenia are planning.

Conflict of interest

None declared.

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We confirm that there has been no significant financial support for this work that could have influenced its outcome.

Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; Uniform Requirements for manuscripts submitted to Biomedical journals.

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