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Comparing Therapeutic Plasma Exchange to Conventional Immunosuppressive Therapy in Refractory Myasthenia Gravis

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Abstract
The myasthenia gravis (MG) condition is an autoimmune disorder that affects the membrane that surrounds the neuromuscular junction and is known as the postsynaptic membrane. It is caused by autoantibodies targeting acetylcholine receptors, muscle-specific kinase, and LRP4. Ocular myasthenia gravis (OMG) is a form of MG characterized by temporary muscle paralysis. Severe MG leads to significant restrictions on daily activities and increased risk of myasthenia crises. Treatment options include intravenous immunoglobulin (IVIG) and plasma exchange (PE). Plasmapheresis (PE) is considered superior due to its quicker response time and higher effectiveness. LPE is a unique medical treatment that combines lymphocyte apheresis with PE techniques. A study involving 236 patients found that LPE can achieve clinical efficacy comparable to or superior to PE while requiring fewer replacements in severe MG cases.
Keywords: Myasthenia gravis (MG), Plasmapheresis (PE), intravenous immunoglobulin (IVIG), Lymphoplasmapheresis (LPE), Ocular myasthenia gravis (OMG), muscle-specific kinase, acetylcholine receptors

Introduction

The myasthenia gravis (MG) condition is an autoimmune disorder that affects the membrane that surrounds the neuromuscular junction and is known as the postsynaptic membrane. It is not a characteristic that is passed down via generations; instead, it is the outcome of things that an individual has learned and experienced over their lives. The prevailing consensus is that the pathophysiological processes observed in most patients are primarily caused by autoantibodies (Abs) that primarily target AChR, MuSK, and low-density LRP4 (2). In addition to the problem that already exists, a small group of patients have demonstrated the presence of autoantibodies, specifically titin-Ab and ryanodine receptor (RyR)-Ab, which attack proteins linked with the muscle in a selective manner (3). Ocular myasthenia gravis (OMG) is a form of myasthenia gravis (MG) that is characterized by temporary muscle paralysis. This specific variant of myasthenia gravis mainly impacts the ocular muscles. This disorder is characterized by the presence of diplopia and ptosis as symptoms. Most patients undergo a gradual deterioration in their health over several years. Myasthenia gravis (gMG) causes symmetrical muscle weakness in the limbs, face, neck, and bulbar region, resulting in a diverse range of symptoms. Dysarthria,

characterized by impaired speech, and dysphagia, characterized by impaired swallowing, are both symptoms experienced by patients as a result of this neurological disorder. Furthermore, patients exhibit challenges in elevating their heads and display indications of muscular debility (5). Myasthenic crises, also known as respiratory muscle paralysis, is a life-threatening medical illness that poses a risk to patients and can potentially endanger their lives (6).

Due to the presence of severe myasthenia gravis, there are substantial restrictions on daily activities and an increased risk of potentially deadly myasthenia crises, which worsens the overall burden of the condition. Therefore, it is crucial that those afflicted with severe myasthenia gravis promptly obtain relief from their symptoms.

Literature Review

Patients with severe myasthenia gravis (MG) have two main treatment choices for achieving a quick clinical response: intravenous immunoglobulin (IVIG) and plasma exchange (PE) (7, 8). After being removed from a patient's blood via an injection, the plasma is replaced with either a colloidal solution or a mixture of colloidal and crystal solutions. The colloidal solution may contain albumin and plasma. A therapy method used in the medical field called plasmaexchange, or PE, may also be used in the colloidal solution. Plasma exchange (PE) treatment for autoimmune illnesses aims to effectively eliminate harmful substances, such as autoantibodies (9). It is the fundamental process that forms the basis of PE treatment. Plasmapheresis (PE) is considered a superior treatment for severe myasthenia gravis (MG) compared to intravenous immunoglobulin (IVIG) due to its quicker response time and higher degree of effectiveness (10).

Lymphoplasmapheresis, also referred to as LPE, is a unique medical treatment that involves the combination of lymphocyte apheresis with the more commonly used plasma exchange (PE) techniques. It removes harmful substances that can cause an immune reaction, such as cell adhesion chemicals, immune-boosting proteins, immune-regulating signaling molecules, and antibodies that target existing cells in the body. Furthermore, it eradicates immune cells that have acquired a susceptibility to specific medications, serving as an added advantage. Nevertheless, this differs from PE. As a result, abnormal immune responses can be better managed and maintained with enhanced efficacy (11). Research conducted between 2011 and 2014 has shown that LPE is beneficial in treating autoimmune disorders such as Guillain-Barré syndrome, steroid-resistant neuromyelitisoptica spectrum illnesses, and severe incurable autoimmune skin diseases. Based on the findings of a previous experiment conducted at our institution, it has been determined that LPE is a secure and efficient technique for controlling the advancement of MG (15).

Material Methods

Inclusion criteria: We conducted a comprehensive search strategy to gather relevant studies and data for our review article. Utilizing databases such as PubMed Central, Google Scholar, Scopus, and others, we focused on identifying literature concerning the incidence of ST-segment elevation myocardial infarction (STEMI) and its equivalents within the emergency medicine domain. By employing Medical Subject Headings (MeSH) and specific keywords like "percutaneous coronary intervention," "cardiogenic shock," and "myocardial infarction," among others, we ensured a systematic approach to locating relevant papers and research articles.

Exclusion criteria:

The data applied to the investigated articles is described below:

1. The article language should be in English as this is the language that is familiar to the author. Articles with other languages are excluded.
2. Articles should be peer-reviewed. So, non-published or reviewed articles are excluded.
3. The thesis is excluded; on the basis that they had not been subjected to formal peer review.
4. The author only had access to the abstracts of the articles.

Following the initial search, we selected studies based on predefined inclusion and exclusion criteria. Criteria included relevance to the topic, publication date, study design, and language. We also reviewed abstracts and full-text articles to determine eligibility for inclusion in the review. Data extraction was performed using a standardized approach. Relevant data items were extracted from each included study. A descriptive method was utilized in the process of synthesizing the findings. This strategy entailed summarizing and analyzing the data from a selection of studies in order to discover recurring themes, patterns, and gaps in the existing body of research. Additionally, we assessed the quality of included studies and considered any limitations in the interpretation of the findings.

Result and Discussion

The first trial group consisted of 236 patients with a diagnosis of severe myasthenia gravis (MG) who were treated with either low-dose plasma exchange (LPE) or plasmapheresis (PE) between November 2016 and January 2022. Treatment was given at Changsha First Hospital, Xiangya Second Hospital, and the Neurology Department of Xiangya Hospital. The medical operation was also carried out at Changsha First Hospital. The following diagnostic standards are applied to diagnose MG: It is empty in the user's text. Changes in strength and a tendency to tire easily are two traits that are commonly linked to muscle weakness. A combination of causes may also result in muscle weakness. The test results show that autoantibodies linked to MG are present. To assist in the diagnosis of patients with negative antibody responses, electromyography and the neostigmine test were utilized (6). These examinations were used to help in patient diagnosis. Patients classified as having severe myasthenia gravis (16) in this research had a Myasthenia Gravis Foundation of America (MGFA) Clinical Classification of Class IV. The MGFA Clinical Classification is used to determine the severity of the condition; Class IV denotes a significant impact on many muscle groups. 38 people were removed from the list of participants. This happened as a result of the participants' failure to supply adequate clinical data. There were 198 people in the final trial group. Of the total number of patients, 123 underwent LPE treatment, while 75 underwent PE treatment. 198 patients signed up to take part in the trial.

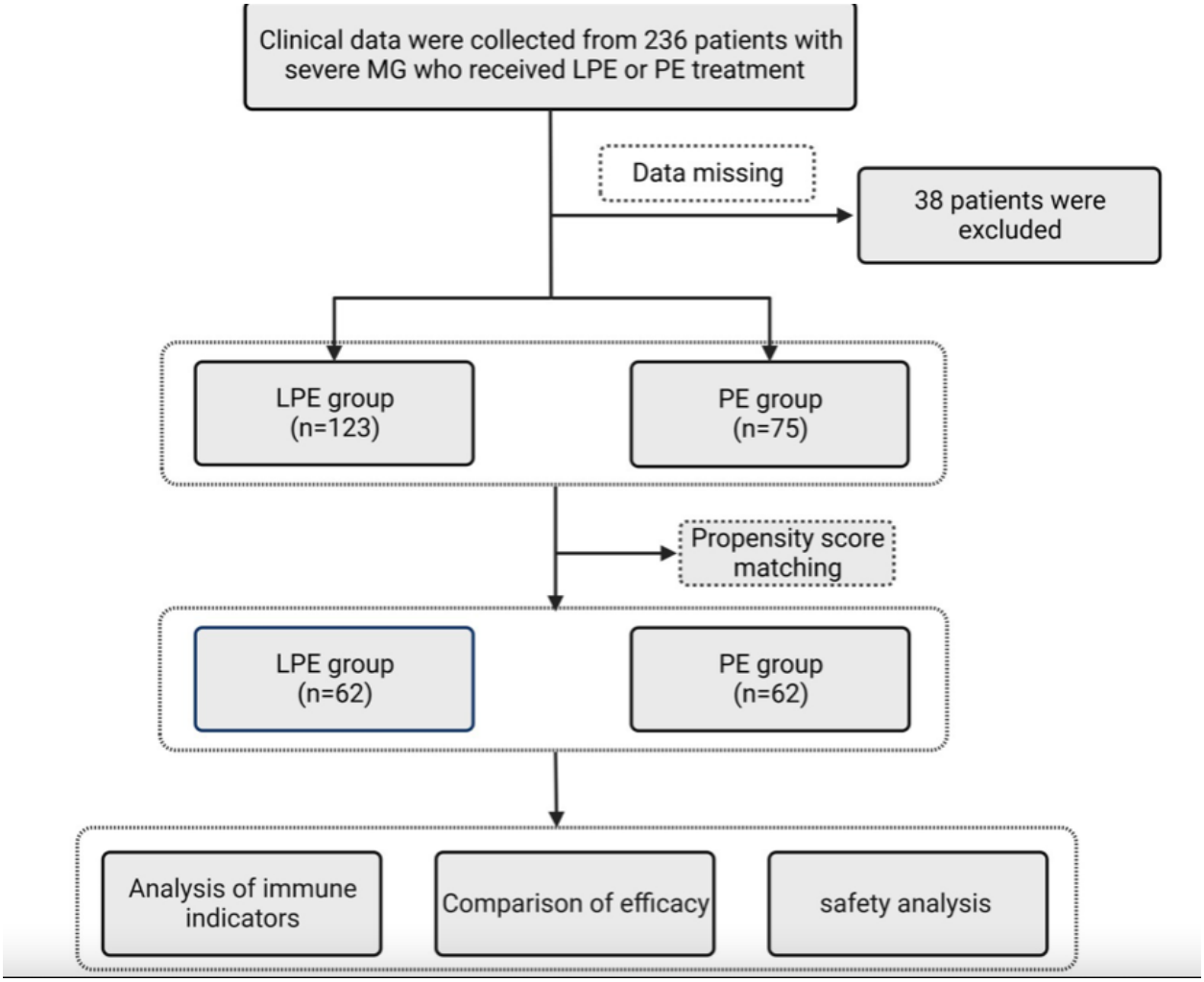

Figure 1: The study's flowchart was created.

An illustration of the procedure that was followed in this research can be found in Figure 1. In Table 1, you will find a summary of the clinical features of the patients who were enrolled in the study. There were a considerable number of female participants in both the physical education (PE) and the low physical education (LPE) groups, with 72.0% and 61.8% of the total, respectively. The LPE group had an average age of 45.24 ± 16.12 years, whereas the PE group had an average age of 46.63 ± 15.95 years across the two groups. Patients with thymomas accompanied with PE patients included 22.7% (17 instances), while patients in the LPE group comprised 20.3% (25 cases). The percentage in the LPE group, on the other hand, was a mere 20.3% (25 cases).

Two hundred and eighty-eight patients in the LPE group and twenty-seven cases (17 instances) in the PE group were among the patients with a history of thymectomy. In contrast, the baseline QMGS for the PE group was reported as 23.03 ± 4.03 points, whereas it was recorded as 23.40 ± 4.25 points for the LPE group. With respect to the autoantibodies associated with MG, the majority of patients in both groups had AChR-Ab. Regardless of the group, this was the situation.

Ninety-two percent of patients in the PE group and eighty-nine point four percent of patients in the LPE group respectively carried this antibody. The proportion of patients in the PE group who got prednisone monotherapy on a synchronous oral immunotherapy regimen differed significantly from the patients in the LPE group (24.0% versus 7.3%, p = 0.001). The statistical analysis indicated that the difference was substantial. Prednisone and tacrolimus were combined to treat 75% of patients in the LPE group; this is a higher percentage than the 54.7% of patients in the control group (p = 0.016). The fact that different facilities had varying tastes when it came to therapeutic medications could be one explanation for this. It's also important to note that patients in the PE group spent an average of 11.85 ± 4.27 days in the hospital, whereas patients in the LEP group spent an average of 11.26 ± 4.19 days there. The statistical significance threshold was not met by any of these differences (p = 0.34).

Statistical analysis

The statistical analysis for this inquiry was conducted using the software SPSS 26.0 (IBM, USA). Instances of categorical variables were demonstrated through the utilization of counts and percentages. The statistical measure employed to express continuous variables was the mean ± standard deviation (SD). The paired t-test and the Wilcoxon signed-rank test were utilized to compare immunological markers and QMGS before and during the intervention. Both of these tests were employed to examine the data. Both the two-sample t-test and the Mann–Whitney U test were utilized to compare the quantitative data acquired from the two groups.

Alternatively, the chi-square test or the Fisher exact test were used to compare qualitative data. Both of these tests were employed. The propensity score matching (PSM) technique was used to address the confounding factors that were present in both groups and achieve balance. The tolerance threshold for this technique was established at 0.03, and the ratio for matching was set at one-to-one. A significance level of 0.05 was selected as the threshold for determining whether there were statistically significant differences in this specific investigation.

Table 1: Pre-propensity score baseline characteristics in PE and LPE patients.

Characteristics	PE (n=75)	LPE (n=123)	p value
Gender (female) (n, %)	54 (72.0%)	76 (61.8%)	0.14
Age (years, mean ± SD)	46.63 ± 15.95	45.24 ± 16.12	0.56
Disease duration (month, mean ± SD)	48.92 ± 68.50	46.64 ± 71.28	0.76
Thymoma (n, %)	17 (22.7%)	25 (20.3%)	0.70
Thymic hyperplasia (n, %)	3 (4.0%)	4 (3.3%)	0.78
History of thymectomy (n, %)	17 (22.7%)	28 (22.8%)	0.98
Other autoimmune diseases (n, %)	15 (20.0%)	24 (19.5%)	0.93
Co-infection (n, %)	22 (29.3%)	30 (24.4%)	0.44
Immunotherapy before treatment (n, %)	42 (56.0%)	66 (53.7%)	0.75
History of myasthenic crisis (n, %)	8 (10.7%)	14 (11.4%)	0.88
MGFA IVb (n, %)	63 (84.0%)	101 (82.1%)	0.73
Baseline QMGS (mean ± SD)	23.03 ± 4.03	23.40 ± 4.25	0.54
AChR-Ab (n, %)	69 (92.0%)	110 (89.4%)	0.55
MuSK-Ab (n, %)	1 (1.3%)	4 (3.3%)	0.40
Titin-Ab (n, %)	20 (26.7%)	26 (21.1%)	0.37
RyR-Ab (n, %)	10 (13.3%)	15 (12.2%)	0.82
Simultaneous oral immune drugs (n, %)			
Prednisone monotherapy	18 (24.0%)	9 (7.3%)	0.001**
Prednisone and tacrolimus	41 (54.7%)	88 (71.5%)	0.016*
Prednisone and mycophenolate mofetil	5 (6.7%)	10 (8.1%)	0.71
Prednisone and azathioprine	3 (4.0%)	5 (4.1%)	0.98
Tacrolimus monotherapy	5 (6.7%)	8 (6.5%)	0.96
Mycophenolate mofetil monotherapy	2 (2.7%)	3 (2.4%)	0.92
Length of stay	11.85 ± 4.27	11.26 ± 4.19	0.34

*$p < 0.05$, **$p < 0.01$.

Conclusion

In conclusion, this study is the first examination to evaluate the effectiveness of PE and LPE in the treatment of MG. Our research suggests that LPE can provide comparable or superior clinical efficacy compared to PE, while requiring fewer replacements in severe cases of MG. This study provides a third piece of evidence supporting the use of LPE in MG. Furthermore, our research has a few limitations. Initially, preventing selection bias was challenging due to the limitations imposed by the retrospective methodology employed in this study. The second problem arises from our inability to conduct a thorough examination of the efficacy of LPE and PE through the integration of many scoring methodologies. Consequently, there were constraints in the available

data, specifically the absence of information regarding scores such as ADL, MGC, and MG-QOL15r. This was the cause of the occurrence. Another aspect to contemplate is that this inquiry did not entail any form of mechanical examination.

Finally, it is important to note that the sample size of this study was relatively small, which could have influenced the presence of bias in the findings. Further, more thorough randomized controlled trials should be done in the future to authenticate the findings of this investigation. Moreover, to enhance the evidence supporting the use of LPE in treating severe MG, it is imperative to conduct a comprehensive inquiry into the therapeutic mechanism underlying LPE treatment for severe MG.

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