REVIEW

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Comparison of intravenous immunoglobulin and plasma exchange as preoperative preparations for thymectomy: A systematic review

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ABSTRACT

Background: Myasthenia gravis is an autoimmune neuromuscular disease. Thymectomy is a recommended procedure for patients with thymoma, in conjunction with medical therapies. Previous research has explored the use of intravenous immunoglobulin (IVIG) and plasma exchange (PLEX) as preoperative interventions. Despite this, there remains a gap in clinicians' understanding of the comparative efficacy of IVIG or PLEX for preoperative optimization. This review aims to evaluate the relative effectiveness of IVIG and PLEX as preoperative preparations for thymectomy.

Methods: This systematic review was conducted in alignment with the Cochrane Handbook, Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), and Synthesis Without Meta-analysis (SWiM) guidelines. Inclusion criteria comprised full-text manuscripts published between January 2000 and August 2024 that compared IVIG and PLEX as preoperative preparations for thymectomy, regardless of study design. Only studies involving human subjects and those that specifically compared the methodology and outcomes of IVIG and PLEX were included. A comprehensive search was performed across six databases. The quality of included studies and their risk of bias were thoroughly assessed.

Results: The initial search yielded 5,780 articles from databases. Following a rigorous screening process, four studies met the inclusion criteria and underwent detailed quality and risk of bias assessment, with all included studies demonstrating good quality. Most studies demonstrated comparable outcomes between IVIG and PLEX regarding ICU stay, hospitalization duration, and intubation outcomes, indicating that the safety of thymectomy was not significantly influenced by the type of immunomodulation. Nevertheless, IVIG tended to be associated with shorter hospitalization duration, while some studies reported lower postoperative intubation rates and shorter preoperative hospitalization compared with PLEX.

Conclusion: Both IVIG and PLEX demonstrated comparable safety profiles during the perioperative period of thymectomy. Although most outcomes were not significantly different between the two interventions, several studies suggested potential advantages of IVIG, including shorter hospitalization duration and lower postoperative intubation rates. Therefore, IVIG may be considered a viable alternative to PLEX for preoperative preparation before thymectomy

Keywords: Intravenous immunoglobulin, myasthenia gravis, plasma exchange, thymectomy.
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INTRODUCTION

Myasthenia gravis (MG) is a rare autoimmune neuromuscular condition affecting individuals across different age groups, with an estimated prevalence of 0.5–20.4 cases per 100,000 population.[1] The underlying pathophysiology of myasthenia gravis is mainly mediated by autoantibodies directed against postsynaptic nicotinic acetylcholine receptors at the neuromuscular junction or against muscle-specific tyrosine kinase (MuSK) receptors in skeletal muscle.[2] The condition may involve various voluntary muscles and commonly presents as fatigable muscle weakness that worsens with continued use and improves after periods of rest.[3] The extrinsic ocular muscles are the most commonly affected, resulting in symptoms such as ptosis and diplopia, often accompanied by fluctuating generalized weakness.[4]

The treatment of myasthenia gravis includes anti-cholinesterase medications and immunosuppressive agents, including corticosteroids, cyclosporine, and azathioprine. However, primary stabilizing treatments are plasma exchange (PLEX) and intravenous immunoglobulin (IVIG).[5,6] These treatments can be used in cases of exacerbation,[7,8] as preoperative preparation,[9] and for patients who do not respond or tolerate immunosuppressive agents.[10,11] Meanwhile, numerous studies[12,13] have reported the effectiveness of PLEX and IVIG in stabilizing the hemodynamic factors, and comparative analyses have not consistently

identified a clear superiority between the two treatments.[14,15] In addition to pharmacological interventions, thymectomy is a surgical approach, particularly for patients with thymoma. This procedure is typically recommended for patients under 60 years old with generalized myasthenia gravis but without ocular myasthenia gravis.[16]

Several studies have explored the effectiveness of IVIG and plasma exchange (PLEX) as preoperative immunomodulatory therapies prior to thymectomy to improve perioperative outcomes in patients with myasthenia gravis.[17] Both of these co-adjuvant therapies have demonstrated potential in improving respiratory function and enhancing muscle strength post-thymectomy.[18] However, the available evidence remains limited and heterogeneous, with variations in study design, sample size, geographical origin, and reported clinical outcomes. As a result, the comparative effectiveness of IVIG and PLEX as preoperative preparation for thymectomy has not been clearly established, leaving uncertainty for clinicians when selecting the optimal immunomodulatory strategy. Consequently, this review aims to evaluate the relative effectiveness of IVIG and PLEX as preoperative preparations for thymectomy.

METHODS

The present systematic review was conducted in accordance with the Cochrane Handbook for Systematic Reviews and followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) and Synthesis Without Meta-analysis (SWiM) reporting guidelines.

Inclusion and exclusion criteria

The inclusion criteria were studies involving patients diagnosed with myasthenia gravis undergoing thymectomy; full-text manuscripts comparing IVIG and PLEX as preoperative preparations for thymectomy regardless of study design, including experimental studies such as clinical trials and observational studies comprising descriptive designs such as case reports and case series, as well as analytical designs such as cross-sectional, case-control, and cohort studies; publications from January 2000 to August 2024; studies involving human subjects; and studies with clearly defined objectives, methodologies, and outcomes related to the comparison of IVIG and PLEX for thymectomy preparation. Studies were excluded if they did not directly compare IVIG and PLEX as preoperative preparations for thymectomy.

Outcomes Evaluated

The primary outcomes assessed included the duration of postoperative intubation or ventilator use (hours), length of stay in the intensive care unit (days), and overall hospitalization duration (days).

Search Methods

A comprehensive literature search was conducted using the following electronic databases, i.e., MEDLINE via PubMed, ScienceDirect, Google Scholar, CENTRAL (Cochrane Central Register of Controlled Trials), ProQuest, and SpringerLink. The search strategy combined Medical Subject Headings (MeSH) terms and free-text keywords related to thymectomy and immunomodulatory therapies. The primary search terms included: ("thymectomy") AND ("intravenous immunoglobulin" OR "IVIG" OR "IGI") AND ("plasmapheresis" OR "plasma exchange" OR "PLEX"). Additionally, to ensure comprehensive coverage, the bibliographies of the included studies were further examined for additional relevant articles.

Data Collection and Analysis

Titles and abstracts retrieved from the electronic databases were independently screened by two reviewers to identify potentially eligible studies. Articles considered relevant were then subjected to full-text review to determine their eligibility according to the predefined inclusion and exclusion criteria. Any discrepancies between the reviewers during the screening and eligibility assessment were resolved through discussion and consensus. If disagreement persisted, a third reviewer was consulted to reach a final decision. This process was conducted to ensure consistency and minimize selection bias in the study selection procedure. Data from the included articles were summarized in a table, outlining key aspects such as the first author, country of origin, study design, sample characteristics, intervention, and outcomes.

Quality assessment

The quality and risk of bias of each included study were initially assessed by the first author and subsequently discussed with the other authors. The Newcastle–Ottawa Scale (NOS) was used to evaluate the methodological quality and risk of bias of cohort studies. The overall scores were interpreted as follows, i.e., studies scoring ≥7 points were classified as a good study, those with scores of 5–6 points were considered a fair study, and studies scoring <5 points were categorized as a poor study.

Randomized clinical trials were evaluated using the modified Jadad scale to determine study quality and potential risk of bias. The total score ranged from 0 to 8, obtained by adding the scores assigned to each assessment item. Trials with scores of 0–3 were categorized as low quality, while those scoring 4–8 were regarded as high quality.

RESULTS

Selection of articles for review

The process of identifying and selecting studies included in this review is illustrated in the PRISMA flow diagram in Figure 1. Initially, 5,780 articles were identified through electronic scientific databases. After removing duplicates, 423 studies were screened based on titles and abstracts. Studies that failed to meet the established inclusion and exclusion criteria were excluded from subsequent evaluation. A total of 187 articles were assessed for eligibility, of which only four were included in this review.

Study characteristics

A summary of the characteristics of the included studies is provided in Table 1. The study designs consisted of three cohort studies and one randomized clinical trial. The included studies published between 2001 and 2022 comparing IVIG and PLEX as preoperative management before thymectomy in myasthenia gravis

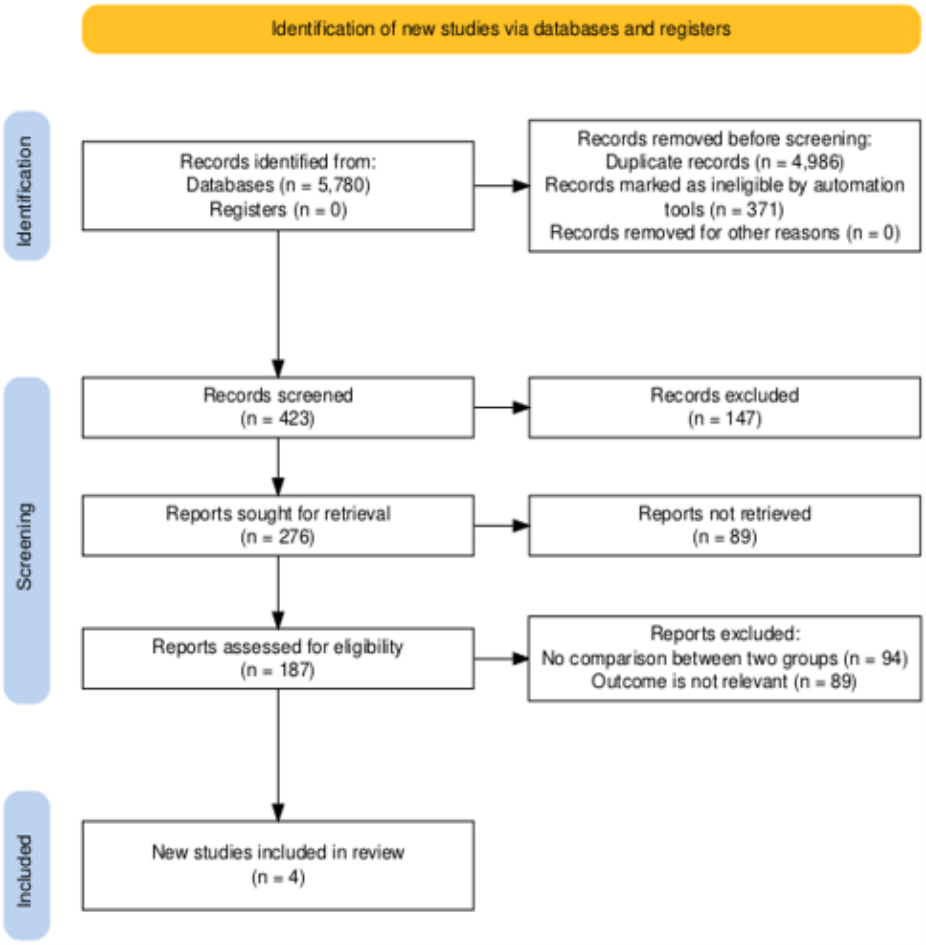


Figure 1. PRISMA Flow Diagram

patients. Most studies, including those by Nellar (2001)[19], Jensen (2008)[9], and Abdelmotaleb (2022)[21], reported no significant differences between IVIG and PLEX regarding ICU stay, hospitalization duration, or intubation outcomes, although IVIG generally showed shorter hospitalization duration. Meanwhile, Alipour-Faz (2017)[20] demonstrated significant benefits of IVIG, including lower postoperative intubation rates, while Abdelmotaleb (2022)[21] also reported significantly shorter preoperative hospitalization in the IVIG group. Each of the included studies underwent quality and risk of bias assessment, with all included studies demonstrating good quality.

Assessment of study validity (Quality assessment and risk of bias)

All included studies made direct comparisons between IVIG and PLEX as preoperative preparations for thymectomy. Table 2 summarizes the quality scores for the cohort studies, all of which scored 7 points (good quality). Table 3 presents the quality assessment for the randomized clinical trial, which scored 5 points (high quality).

DISCUSSION

In addition to pharmacological treatments, the thymectomy procedure is widely used to manage patients with myasthenia gravis (MG). Early surgical intervention plays a critical role in achieving and maintaining remission in MG patients. Immunomodulation as a preoperative preparation for thymectomy can be administered using either PLEX or IVIG, though PLEX is more commonly used. This review discusses four studies that compared the efficacy of IVIG and PLEX as preoperative preparations for thymectomy.

The prospective cohort study in Cuba by Nellar et al. (2001).[19] reported that the postoperative intubation period was statistically shorter in patients receiving IVIG before the thymectomy procedure. The endotracheal tube was removed 14.01 hours after thymectomy in the IVIG group, whereas in the plasmapheresis group, it was removed later at 17.24 hours. However, the difference was not statistically significant (p-value = 0.271). In contrast, a randomized clinical trial in Iran by Alipour-Faz et al. (2017) observed significant differences. In the PLEX group, 7 out of 12 patients were postoperatively intubated, with a median intubation duration of 13 hours, while in the IVIG group, only two patients were intubated (p-value = 0.01). Therefore, the number of intubated patients and the intubation period were statistically shorter in the group of patients receiving IVIG as preoperative preparation.[20]

A trend towards shorter hospital stays with IVIG compared to PLEX was identified in a retrospective cohort study in Egypt by Mohamed Abdelmotaleb (2022). The duration of hospitalization preoperatively was significantly shorter for the IVIG group (1.86 ± 1.21 days) compared to the PLEX group (4.43 ± 2.30 days) (p-value = 0.02). The significant difference is likely due to the IVIG being administered as one dose or two doses over two consecutive days, requiring only 1 or 2 days before thymectomy. In contrast, the PLEX group required 4 to 6 days before thymectomy, as two or three sessions of PLEX were needed, with sessions spaced every other day. The duration of hospitalization postoperatively did not show any significant difference between the two groups, with 4.29 ± 0.49 days for IVIG versus 4.71 ± 0.95 days for PLEX (p-value = 0.31).[21]

The cohort study by Nellar et al. (2001)[19] indicated that the PLEX group had a longer stay in both the ICU (4.34 days) and the general ward (7.34 days) compared to the IVIG group (3.36 days in ICU and 6.57 days in the ward). However, these differences were not statistically significant (p = 0.270 for ICU stay and p = 0.320 for ward stay). Similarly, the retrospective cohort study in Canada by Paul and Bril (2008)[9] showed that the IVIG group before thymectomy had a shorter

Table 1. Study Characteristics

No.	First author, country, year	Study design	Sample characteristic	Intervention	Outcome
1.	Nellar, Jesus Perez et al. Cuba. 2001	Cohort prospective	71 patients (33 patients received IVIG, and 38 patients underwent PLEX)	The IVIG group (n = 33) received a total dose of 2 g/kg/day of IVIG, with two-thirds of the dose administered during the week prior to the operation, and the remaining dose given two days after the operation. The PLEX group (n = 38) underwent three sessions of approximately 3,000 ml each, administered on alternate days during the week before the operation, with two similar replacements during the two days following the operation.	In the IVIG-treated group, the endotracheal tube was removed 14.01 hours post- thymectomy, whereas in the PLEX-treated group, it was removed later at 17.24 hours. However, the difference was not statistically significant (p-value = 0.271). The group treated with plasmapheresis had a longer stay, both in the ICU (4.34 days) and in the room (7.34 days), compared with the group treated with IVIG, which had stays of 3.36 days in the ICU and 6.57 days in the room. However, the differences were not significant (p-value = 0.270 for ICU stay and p-value = 0.320 for room stay).
2.	Jensen Paul and Bril Vera. Canada. 2008	Cohort retrospective	35 patient charts were reviewed (9 patients received IVIG, and 26 patients underwent PLEX)	No specified dose regimen was detailed for either intervention group.	A trend towards shorter hospital stays was observed with IVIG, averaging 2.2 ± 1.9 days, compared to 3.3 ± 1.2 days for PLEX (p-value = 0.16).
3.	Abdelmotaleb, M S. Egypt. 2022	Cohort retrospective	14 patients (7 patients received IVIG, and 7 patients underwent PLEX)	The IVIG group (n = 7) received 1 g/kg/day of IVIG as a single dose, with some cases requiring a second dose on two consecutive days based on the neurologist's evaluation. To control possible allergic side effects of IVIG, patients were premedicated with diphenhydramine (50 mg) and acetaminophen (650 mg) tablets before the infusion. The PLEX group (n = 7) underwent two or three sessions of 1 L PLEX with 5% albumin replacement fluid administered every other day, according to the neurologist's assessment.	The preoperative duration of hospitalization was significantly different between the two groups. The mean preoperative hospitalization duration was 1.86 ± 1.21 days for the IVIG group compared to 4.43 ± 2.30 days for the PLEX group (p-value = 0.02). The postoperative hospitalization duration did not show any significant difference between the two groups, with 4.29 ± 0.49 days for IVIG versus 4.71 ± 0.95 days for PLEX (p-value = 0.31). Additionally, the ICU length of stay did not show any significant difference between the two groups, with 1.29 ± 0.49 days for IVIG versus 1.14 ± 0.38 days for PLEX (p-value = 0.55). One of the seven patients in each group required postoperative intubation and mechanical ventilation.
4.	Alipour-Faz A et al. Iran. 2017	Randomized clinical trial	24 patients (12 patients received IVIG, and 12 patients underwent PLEX)	The IVIG group (n = 12) received 1 g/kg/day of IVIG for two consecutive days. To control potential side effects of IVIG, including urticaria, dyspnoea, wheezing, low-grade fever, and post-infusion headaches, patients were premedicated with diphenhydramine (50 mg) and acetaminophen (650 mg). The PLEX group (n = 12) underwent five sessions of 1 L plasma exchange with 5% albumin replacement fluid administered every other day. Both treatments were conducted 10–30 days prior to thymectomy.	In the PLEX group, 7 out of 12 patients required postoperative intubation, with a median intubation duration of 13 hours, while in the IVIG group, only two patients were intubated (p-value = 0.01). The duration of hospitalization did not show any significant difference between the two groups, with 20.27 ± 8.42 days for IVIG versus 21.08 ± 5.29 days for PLEX (p-value = 0.78). Additionally, the ICU length of stay showed no significant difference between the two groups, with 2.33 ± 1.49 days for IVIG versus 3.75 ± 3.10 days for PLEX (p-value = 0.16).

Table 2. Newcastle-Ottawa Scale for Cohort Study

No	Author (Year)	Selection				Comparability	Outcome			Total
		1	2	3	4		1	2	3	
1.	Nellar et al., (2001)	*		*	*	*	*	*	*	7
2.	Jensen and Bril (2008)	*		*	*	*	*	*	*	7
3.	Abdelmotaleb (2022)	*		*	*	*	*	*	*	7

The maximum score for comparability was 2; Selection: (1) representativeness, (2) selection of non-exposed, (3) ascertainment of exposure, (4) demonstration that the outcome was not present at the beginning; Outcome: (1) assessment of the outcome, (2) follow-up long enough, (3) adequacy of follow-up.

Table 3. Modified JADAD scale for Randomized Clinical Trial (Alipour-Faz A et al., 2017)

Eight items	Answer	Score
Was the study described as randomized?	Yes	+1
Was the method of randomization appropriate?	Yes	+1
Was the study described as blinding?	No	0
Was the method of blinding appropriate?	Not described	0
Was there a description of withdrawals and dropouts?	No	0
Was there a clear description of the inclusion/exclusion criteria?	Yes	+1
Was the method used to assess adverse effects described?	Yes	+1
Was the method of statistical analysis described?	Yes	+1
Total Score		+5

hospital stay (2.2 ± 1.9 days) compared to the PLEX group (3.3 ± 1.2 days). Although the difference was not statistically significant (p-value = 0.16), the results suggest that IVIG had comparable efficacy to PLEX as a preoperative preparation, making it a reasonable alternative before thymectomy.

A randomized clinical trial in Iran by Alipour-Faz et al. (2017)[20] also investigated the efficacy of IVIG versus PLEX as a preoperative preparation before thymectomy. The study found that postoperative outcomes, including ICU length of stay, duration of surgery, and overall hospitalization, were shorter in the IVIG group. The mean ICU stay was 2.33 ± 1.49 days for the IVIG group compared to 3.75 ± 3.10 days for the PLEX group (p-value = 0.16). The mean hospitalization duration was 20.27 ± 8.42 days for the IVIG group and 21.08 ± 5.29 days for the PLEX group (p-value = 0.78). Despite the lack of statistical significance, the authors concluded that IVIG might be more effective and efficient as a preoperative preparation.

PLEX is widely recognized as the gold standard for preoperative optimization in MG patients, particularly those experiencing clinical deterioration. However, its administration poses several challenges, including high hospital costs, the need for specialized apheresis devices, trained medical staff, and the necessity of advanced centres for treatment. In contrast, IVIG is more accessible, being available in most inpatient or outpatient settings, and does not require specialized equipment or trained medical staff for its administration. The safety of the thymectomy procedure was not dependent on the type of immunomodulation, as previous studies confirmed the comparable safety of immunomodulation with either type of treatment.

Heatwole et al. (2011)[22] also conducted a comparative cost-minimization analysis between IVIG and PLEX as primary immunomodulatory methods for MG crisis. The study examined hospital costs associated with these two methods and found that the costs for IVIG were $22,326 less than those for PLEX. They concluded that the administration of IVIG might be a short-term cost-minimizing treatment compared with PLEX.[22]

Current clinical guidelines and recent literature emphasize the importance of optimizing patients with myasthenia gravis before surgical procedures to reduce the risk of perioperative complications, particularly respiratory failure and myasthenic crisis. Immunomodulatory therapies such as plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) are commonly recommended in patients with significant disease severity or those at high risk of postoperative respiratory compromise. Both therapies act by reducing circulating pathogenic antibodies and improving neuromuscular transmission, thereby stabilizing patients prior to surgery.

The findings of the present review are consistent with previous studies suggesting that both IVIG and PLEX provide comparable efficacy in perioperative management of myasthenia gravis. While PLEX has traditionally been considered the preferred option in severe cases due to its rapid antibody removal, IVIG has emerged as a practical alternative because of its easier administration and broader availability. This is particularly relevant in clinical settings where access to specialized apheresis equipment may be limited. IVIG appears to be effective and efficient as a preoperative optimization method for thymectomy in some patients. It represents a promising alternative treatment option to improve outcomes after surgery. Therefore, the choice between IVIG and PLEX may depend not only on clinical factors but also on institutional resources and patient-specific considerations.

This review has several limitations that should be considered when interpreting the findings. First, only a limited number of studies met the inclusion criteria, which may reduce the strength and generalizability of the conclusions. Second, the included studies varied in terms of study design, sample size, and outcome measurements, which limited the ability to perform a quantitative meta-analysis. Third, most studies involved relatively small patient populations, which may affect the statistical power of the reported outcomes. Therefore, larger and well-designed prospective studies are needed to provide more robust evidence regarding the

optimal preoperative immunomodulatory strategy for thymectomy in patients with myasthenia gravis.

CONCLUSION

Immunomodulatory therapies are important components in the management of patients with myasthenia gravis undergoing thymectomy. Both plasma exchange (PLEX) and intravenous immunoglobulin (IVIG) may be used as preoperative optimization strategies to reduce perioperative complications. The findings of this review suggest that IVIG and PLEX demonstrate comparable perioperative outcomes. Although several studies suggested potential advantages of IVIG, including shorter hospitalization duration and lower postoperative intubation rates, these findings should be interpreted with caution given the limited number of available studies. Further well-designed prospective studies are needed to establish stronger evidence regarding the optimal preoperative immunomodulatory approach.

DISCLOSURE

ETHICAL APPROVAL

Ethical approval for this study was obtained from the Medical and Health Research Ethics Committee, Faculty of Medicine, Universitas Palangka Raya.

FUNDING

Nil.

CONFLICT OF INTEREST

There is no conflict of interest.

AUTHOR CONTRIBUTION

All authors contributed to the study conception, design, and supervision. They were also involved in manuscript preparation and approved the final version for submission.

GENERATIVE AI (GENAI) DISCLOSURE

The authors declare that no generative artificial intelligence (GenAI) tools or AI-assisted technologies were used in the conception, writing, analysis, or editing of this manuscript. All work was conducted solely by the authors.

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