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Original article

Outcome of Thymectomy in Myasthenia Gravis Patients

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Abstract:

Background: Myasthenia gravis (MG) impairs voluntary muscle function by targeting the postsynaptic acetylcholine receptors, causing weakness and fatigue in the affected muscle group. This study aimed to assess the outcomes of thymectomy in MG patients, measure the extent of clinical improvement post-thymectomy by analysing changes in disease stage and medication needs, and identify prognostic factors that can aid in determining the most suitable patient selection. **Methods:** This prospective study was carried out on 53 patients aged greater than or equal to 18 years old, both sexes, scheduled for MG and underwent transsternal and VATS total thymectomy. Before surgery, each patient was evaluated by the neurologist and underwent a standard chest x-ray and a chest computed tomography. Both VATS and transsternal thymectomy were used as the surgical options in our study. **Results:** The majority of patients- who achieved full clinical remission- were classified under Osserman stages I, IIA, and III. In terms of the relationship between prognostic factors and complete clinical remission, females had a more favorable outcome following thymectomy (P-value = 0.019). Additionally, younger age was associated with better remission outcomes compared to older age groups (P-value < 0.001). **Conclusions:** Thymectomy is recommended for patients younger than 60 years with non-thymomatous, generalized AChR antibody-associated myasthenia gravis. The early-onset MG, severe MG, female sex, and thymic hyperplasia are important factors helping to obtain better postoperative outcome. Thymectomy can reduce patient' s need for medication and the severity of MG regardless of age, sex, severity, or length of sickness, or thymic masses.

Keywords: Myasthenia gravis; Thymus; Thymectomy; Osserman classification; Remission.

Introduction

Myasthenia Gravis (MG) is an autoimmune neuromuscular illness that mostly affects voluntary muscles and is characterized by muscle weakening and tiredness. It is caused by the development of autoantibodies that target the neuromuscular junction and disrupt nerve impulse transmission to the muscles. It is believed that MG is caused by a combination of genetic susceptibility, environmental factors, and immune dysregulation [(1)].

The thymus, a gland located beneath the sternum in the upper chest, plays a crucial role in the development of MG. Seventy to eighty percent of MG patients have a thymic abnormality, such as thymic hyperplasia or thymoma (a tumor of the thymus). The thymus is hypothesized to contribute to the formation of autoantibodies in MG through its role in the development of T-lymphocytes [(2)].

The surgical removal of the thymus, or thymectomy, has been identified as a viable therapy option for MG. The rationale for thymectomy is based on the concept that self-reactive T-cells, which play a major role in the development of multiple myeloma (MG), are created and mature in the thymus. By removing the thymus, the source of autoantibody synthesis can be removed, potentially resulting in an improvement in the clinical condition of MG patients [(3)].

Transsternal (median sternotomy), transcervical, video-assisted thoracoscopic surgery (VATS), and robotic-assisted procedures can all be used to accomplish thymectomy. Considerations such as thymic pathology, surgeon expertise, and patient characteristics influence the choice of technique [(4)].

Evaluation of thymectomy outcomes in MG patients is of the utmost importance. It enables clinicians and researchers to quantify the degree of clinical improvement following thymectomy and evaluate the procedure's effect on disease progression. The success of thymectomy can be objectively determined by examining changes in illness stage, commonly characterized using methods such as the Myasthenia Gravis Foundation of America (MGFA) classification, and medication necessity (e.g., dosage reduction or discontinuation) [(5)].

In addition, finding predictive markers linked with thymectomy outcomes is essential for selecting the optimal patients. Prognostic factors are patient traits or disease-related variables that predict the probability of a positive response to thymectomy. Age, disease duration, intensity of MG symptoms, presence of thymoma, and specific autoantibody profiles may be among these factors. Understanding these prognostic indicators can assist doctors in making informed decisions regarding the surgical therapy of MG, which may result in improved patient outcomes and personalized treatment regimens [(6)].

Therefore, the purpose of this study was to evaluate the results of thymectomy for MG patients, quantify the degree of clinical improvement after thymectomy by evaluating changes in stage and medication requirement, and identify prognostic factors that may be helpful in determining the best patient selection.

Patients and Methods

This prospective study was conducted on 53 patients aged greater than or equal to 18 years old, both sexes, scheduled for MG who were admitted and then underwent transsternal and VATS total thymectomy during the period of January 2017 to January 2022 at king Fahad Armed Forces Hospital, Jeddah. The study was done after approval from the Ethical Committee Benha University Hospitals (approval code: RC 20-5-2023), also informed consent was taken from all participants included.

Preoperative data collection involved obtaining a comprehensive medical history, including information on age, sex, Osserman stage, smoking history, laboratory studies, comorbidities, medication requirements, duration of the disease, and any coexistent medical conditions.

Prior to surgery, each patient underwent assessment by a neurologist based on their clinical complaints, a positive response to edrophonium chloride, and electromyography tests.

The modified Osserman classification was used to stage each case clinically. Surgical treatment was indicated for patients with persistent generalized myasthenia gravis despite medication, persistent ocular myasthenia gravis despite medication, or the presence of a thymoma as detected by computed tomography.

All patients underwent standard chest X-ray and chest computed tomography scans prior to surgery. Laboratory procedures, including radio-immunoassays for acetylcholine receptor antibody levels, immunoglobulin levels, serum complement tests, thyroid function tests, and serum investigations for antithyroid antibodies, were also performed.

A total of 53 patients underwent median, transsternal, and video-assisted thoracoscopic surgery (VATS) thymectomy. The thymic tissue and anterior mediastinal fat were removed from the lower limit of the pericardium to the superior extension of the cervical thymus and from one phrenic nerve to the other. In cases involving invasive thymoma, efforts were made to remove all affected tissue.

Surgical procedures

Two types of surgical approaches were used, VATS and transsternal approaches and all were performed under general anesthesia. After the surgery, each patient received post-operative care in an intensive care unit and supported with mechanical ventilation. Patients who were previously receiving anticholinesterase inhibitors (AchEI) were given these medications one hour before extubation. The time taken for extubation, any abnormalities or issues related to the thymus, and the length of hospital stay were recorded after the surgery. Patients were followed up for varying durations, with an average follow-up period of 2.5 years. During the follow-up, a neurologist conducted interviews with all patients to assess their exercise tolerance, occupation, Osserman stage, medication requirements, challenges faced, and duration of follow-up.

The patients' outcomes after thymectomy were evaluated using the Milichat and Dodge criteria for follow-up assessment. These criteria categorized the patients' responses into several grades:

(a) Complete clinical remission: Patients who experienced a complete disappearance of symptoms and did not

require anticholinesterase inhibitor medication for more than 90 days. (b) Significant clinical improvement: Patients who showed a noticeable improvement in their clinical condition, leading to a reduction in medication dosage. (c) Moderate clinical improvement: Patients who demonstrated a moderate improvement in their clinical status but still required medication to manage their symptoms. (d) No improvement or stable clinical status: Patients who did not experience any improvement in their clinical condition and remained in a stable state without significant changes. (e) Clinical worsening: Patients who experienced a worsening of their symptoms despite being on the same medication dosage or requiring an increased dosage. These patients might need additional or alternative medications to manage their deteriorating condition.

Statistical analysis

The statistical analysis was performed using SPSS v28 (IBM©, Armonk, NY, USA). For quantitative parametric data, the mean and standard deviation (SD) were used to present the results. Quantitative non-parametric data were presented as the median and interquartile range (IQR), which represents the middle 50% of the data. Qualitative variables were described using frequency and percentage (%), and the Chi-square test was utilized for their analysis. A two-tailed P value of less than 0.05 was considered statistically significant, indicating a significant difference or association between variables.

Results

In the study, a total of 53 patients were included, with 28 (52.83%) being males and 25 (47.17%) being females. The average age of the patients was 37.1 ± 8.05 years. Regarding the time elapsed from diagnosis to the operation, 36 patients (67.92%) had a duration of 2 years or more, while 17 patients (32.08%) had a duration of less than 2 years. The mean duration of hospital stay for the patients was 15.4 ± 4.45 days. The median follow-up period, which represents the midpoint of the observed time spans, was 1 month, with a range of 0.6 to 4 months. Among the studied patients, 6 (11.32%) patients had DM, 1 (1.89%) patient had HTN, 5 (9.43%) patients had hyperlipidemia, 3 (5.66%) patients had thyrotoxicosis and 1 (1.89%) patient had pulmonary tuberculosis. Regarding Osserman classification,11 (20.75%) patients were grade I, 22 (41.51%) patients were grade IIA, 13 (24.53%) patients were grade IIB, 3 (5.66%) patients were grade III and 4 (7.55%) patients were grade IV. Regarding the surgical approach, 45 (84.9%) patients underwent VATS and 40 (75.5%) underwent transsternal thymectomy, Table (1).

Before surgery, all patients were on medication,21 (39.62%) patients were on Pyridostigmine, 14 (26.42%) patients were on Pyridostigmine + Azathioprine, 12 (22.64%) patients were on Combination + pheresis, 3 (5.66%) patients were on steroids and 3 (5.66%) patients were on Pyridostigmine + steroids. After surgery, only 7 (13.21%) patients were on Pyridostigmine, 8 (15.09%) patients were on Pyridostigmine+ Azathioprine and 7 (13.21%) patients were on Combination + pheresis. After thymectomy, medication requirement in patients of myasthenia gravis decreases significantly (P <0.001), Table (2), Figure (1).

On macroscopic examination, 6 (11.32%) patients had cyst and 47 (88.68%) patients

had normal findings. Regarding the neurological examination at baseline, 3 (5.66%) patients had bulbar weakness, 5 (9.43%) patients had bulbar and ocular weakness, 7 (13.21%) patients had bulbar and muscular weakness, 20 (37.74%) patients had ocular weakness, 5 (9.43%) patients had ocular and muscular weakness, 4 (7.55%) patients had muscular weakness and 9 (16.98%) patients had bulbar, ocular, and muscular weakness, Table (3).

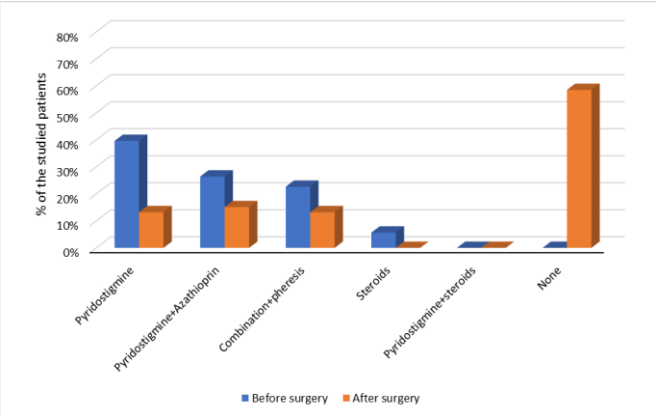

Figure 1: Medication used by the studied patients before and after surgery.

Table 1: Demographic data, comorbidities and classification of patients into grades based on Osserman classification.

		n = 53
Age (years)		37.1 ± 8.05
Sex	Male	28 (52.83%)
	Female	25 (47.17%)
Time elapsed	2 years	36 (67.92%)
	> 2 years	17 (32.08%)
Hospital stays (days)		15.4 ± 4.45
Follow-Up (months)		1 (0.6-4)
Comorbidities	DM	6 (11.32%)
	HTN	1 (1.89%)
	Hyperlipidemia	5 (9.43%)
	Thyrotoxicosis	3 (5.66%)
	Pulmonary tuberculosis	1 (1.89%)
Osserman classification	Eye (I)	11 (20.75%)
	Mild generalized disease (IIA)	22 (41.51%)
	Disease moderate severity generalized (IIB)	13 (24.53%)
	Acute and progressive disease (III)	3 (5.66%)
	Severe disease and late (IV)	4 (7.55%)
Surgical approach	VATS	45 (84.9%)
	Transsternal	40 (75.5%)

Data are presented as mean ± SD, median (IQR) or frequency (%). DM: diabetes mellitus, HTN: hypertension, VATS, video-assisted thoracoscopic surgery.

Table 2: Medication used by the studied patients before and after surgery.

	Before surgery (n=53)	After surgery (n=53)	P value
Pyridostigmine	21 (39.62%)	7 (13.21%)	**<0.001***
Pyridostigmine + Azathioprine	14 (26.42%)	8 (15.09%)	
Combination + pheresis	12 (22.64%)	7 (13.21%)	
Steroids	3 (5.66%)	0 (0%)	
Pyridostigmine + steroids	3 (5.66%)	0 (0%)	
None	0 (0%)	31 (58.49%)	

Data are presented as frequency (%). *: statistically significant as P value <0.05.

Table 3: Macroscopic, and neurological findings of the studied patients.

	n = 53
Macroscopic findings	
Cyst	6 (11.32%)
Normal	47 (88.68%)
Neurological findings at baseline	
Bulbar	3 (5.66%)
Bulbar + ocular	5 (9.43%)
Bulbar + muscular weakness	7 (13.21%)
Ocular	20 (37.74%)
Ocular + muscular weakness	5 (9.43%)
Muscular weakness	4 (7.55%)
Bulbar + muscular weakness + ocular	9 (16.98%)

Data are presented as frequency (%).

The postoperative microscopic findings of the thymus revealed the following findings: 15 (28.3%) patients showed hyperplasia of the thymus, 9 (16.98%) patients had thymoma, 3 (5.66%) patients had thymic carcinoma or atrophy, and 26 (49.06%) patients had a normal thymus, Table (4).

Regarding the postoperative complications, right sided pneumothorax occurred in 1 (1.89%) patient, left lower lobe pneumonia occurred in 2 (3.77%) patient, surgical wound infection occurred in 1 (1.89%) patient and severe myasthenic crisis occurred in 8 (15.09%) patients. As late complications, thymoma recurrence occurred in 1 (1.89%) patient and sinus over sternal region occurred in 1 (1.89%) patient.

Patients experiencing severe myasthenic crises were provided with ventilatory support, intubation, multiple plasmapheresis cycles, prednisolone, and anticholinesterase medications after the operation. Among eight patients, four achieved remission, two showed improvement, and unfortunately, two patients passed away. The mortality rate for hospitalized patients with Osserman grade IIB experiencing myasthenic crises was 2.5 percent. Two patients developed disseminated intravascular coagulation, followed by septicemia, resulting in their death on the sixth day after the operation. One patient required tracheostomy and prolonged ventilation, along with multiple sessions of plasmapheresis and steroid treatment, but unfortunately passed away on the 100th day after the operation. No postoperative deaths were reported during the follow-up period.

The surgical outcomes were analyzed based on the Osserman staging of the patients. The majority of patients who achieved full clinical remission were classified under Osserman stages I, IIA, and III, Table (6).

In terms of the relationship between prognostic factors and complete clinical remission, it is noteworthy that out of the patients who achieved complete clinical remission, 21 were females and 14 were males. This indicates that females had a more favorable outcome following thymectomy (P-value = 0.019). Additionally, based on our data, younger age was associated with better remission outcomes compared to older age groups (P-value < 0.001). Interestingly, neither the histological characteristics of the removed thymus nor the duration of myasthenia gravis were found to be related to the outcomes of thymectomy in this study.

Table 4: Postoperative microscopic findings of thymus.

	n = 53
Hyperplasia of thymus	15 (28.3%)
Thymoma	9 (16.98%)
Thymic carcinoma, atrophy	3 (5.66%)
Normal thymus	26 (49.06%)

Data are presented as frequency (%).

Table 5: Incidence of complications in the studied patients.

	n = 53
Postoperative complications	
Right sided pneumothorax	1 (1.89%)
Left lower lobe pneumonia	2 (3.77%)
Surgical wound infection	1 (1.89%)
Severe Myasthenic crisis	8 (15.09%)
Late complications	
Thymoma recurrence	1 (1.89%)
Sinus over sternal region	1 (1.89%)

Table 6: Surgical outcomes of the studied patients.

Class/Grades	**Number of patients**	**Remission Improvement**	**No improvement**	**Worse**	**Death**
I	11	9	2		
IIA	22	20	2	2	
IIB	13	8	5	2	2
III	3	2	1		
IV	4	2	2		

Discussion

In 1939, Alfred Blalock and his colleagues achieved a successful thymic cyst removal from the thymus of a 26-year-old patient with myasthenia gravis, marking the inception of thymectomy for this condition. Myasthenia gravis is an autoimmune disorder characterized by the attachment of antibodies to acetylcholine receptors, causing disruption in

neuromuscular transmission. The highest incidence of this condition is observed in women in their thirties and forties, as well as men in their sixties and seventies. Typically, the initial manifestation of myasthenia gravis occurs in the eyes, with approximately 80 percent of patients experiencing widespread muscle weakness [(7)].

Myasthenia gravis is treated with anticholinesterase medicines, steroids, immunosuppressive medications, and plasmapheresis to reduce serum antibody concentration [(8)]. A complete clinical remission rate as low as 18% after medical treatment has been reported in [(9, 10)] and (11) studies. Surgical treatment has grown in popularity, with clinical remission rates as high as 42% and clinical improvement rates as high as 94% [(12,13)].

The transsternal technique for thymectomy is a conventional treatment method, and we employed it to completely remove all thymic tissue, including adipose tissue in the anterior mediastinum, as thymic tissue extends beyond the typical thymus capsule [(14, 15)].

Since the induction of video-assisted thoracoscopic surgery (VATS) for thymectomy in 1992, several studies have shown that VATS thymectomy reduces intraoperative blood loss, injury to surrounding tissues, postoperative pain, and fewer postoperative complications [(16)].

The majority of research findings indicate the effectiveness of thymectomy in treating patients with myasthenia gravis. A randomized clinical trial conducted by a study [(17)] provided evidence supporting the positive impact of thymectomy on clinical outcomes in myasthenia patients. Additionally, a study [(18)] highlighted the beneficial effects of thymectomy in patients with moderate and advanced myasthenia gravis. A study [(19)] discovered that thymectomy was particularly effective in the early stages of the disease, with reduced effectiveness observed in surgeries performed during later stages. This reduced effectiveness may be attributed to the irreversible destruction of acetylcholine receptors.

Our findings demonstrate a significant decrease in medication requirement for myasthenia gravis patients after thymectomy. In our study, we observed a strong relationship between thymectomy and a reduced need for post-operative medication. These results align with the study conducted by a study [(20)], where patients with thymoma did not exhibit a poorer response to thymectomy compared to those with non-neoplastic thymus glands, which is consistent with the findings of previous study [(21)].

The current study also found that earlier operations resulted in better recovery. Other

factors correlated with better prognosis were ages of less than 30 years and being a woman. However, pathology did not correlate with the outcome.

Numerous studies have reported a higher degree of improvement in female patients [(22, 23)], which is consistent with the findings of previous study [(20)]. However, in their study, age did not show a correlation with the treatment outcome, despite previous literature suggesting that young adults have a higher rate of complete clinical remission [(24, 25)].

The pathological examination of the thymus following thymectomy has been identified as closely linked to the treatment outcome. Hyperplastic thymus has been associated with a higher rate of complete clinical remission [(26, 27)]. However, in the study conducted by a study [(20)], the

pathology findings did not correlate with the treatment outcome. They concluded that patients with thymoma did not exhibit a poorer response to thymectomy compared to those with non-neoplastic thymus glands, which aligns with the findings of previous study [21].

In the study conducted by a study [20], patients in stages I, IIA, and III experienced a significantly higher level of clinical improvement after thymectomy compared to patients in stages IIB and IV. Previous studies investigating the impact of preoperative Osserman stage on post-thymectomy clinical improvement have yielded mixed findings [28, 29]. A study [30] reported a remission rate of 51% in stage IIA disease and 40% in stage IIB. A study [11] demonstrated greater improvement in patients with mild generalized symptoms. However, other researchers have not found a significant difference in outcomes based on preoperative stage [31].

Thymectomy for patients with ocular involvement in myasthenia gravis is a topic of ongoing debate [32]. Without treatment, approximately two-thirds of these patients will progress to generalized myasthenia gravis. Two studies [11] and [33] strongly support thymectomy as a recommended approach for ocular myasthenia gravis. Similarly, we also endorse thymectomy as a suitable treatment option for ocular myasthenia gravis.

Our study has limitations including single center study with relatively small sample size.

Conclusions

Thymectomy is recommended for patients younger than 60 years with non-thymomatous, generalized AChR antibody-associated myasthenia gravis. Patients with early-onset, severe MG, female sex, and thymic hyperplasia-benefit the most. Osserman Class IIA and III patients derive the greatest benefit from thymectomy. This procedure can decrease the need for medication and alleviate the severity of myasthenia gravis, regardless of age, sex, disease severity, duration, or thymic masses. For cases with thymoma, surgical resection should be performed whenever possible.

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