Original Article

Long-Term Outcomes after Thymectomy for Myasthenia Gravis

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Objective: To investigate the long-term clinical outcomes, including complete remission rate, and the prognostic factors after thymectomy in patients with myasthenia gravis.

Materials and Methods: A total of 183 patients with generalised myasthenia gravis who underwent thymectomy from January 1993 to December 2013 were retrospectively reviewed. Of these, 113 patients had complete follow-up for more than 10 years that could be enrolled for long term complete stable remission rate analysis. 42 cases (23%) were male patients and 141 cases (77%) were female patients. Preoperative and postoperative patient evaluations were based on MGFA classification, including complete stable remission, minimal manifestation, improved, unchanged and worsening. Complete remission was defined as the patient being asymptomatic with normal strength without medication at a 10-year follow-up.

Results: Trans-sternal thymectomy was performed in 94% of patients. Histological analysis revealed 62% of patients had thymic hyperplasia and 14% of patients had thymoma. According to MGFA postoperative statuses, complete stable remission was presented in 47.5%, minimal manifestation in 12%, improved in 31%, unchanged in 5.5%, and worsening in 1.6%. The complete stable remission rate at a 10-year follow-up was 51%. There were no significant prognosis factors for complete stable remission.

Conclusion: Trans-sternal thymectomy is an effective modality of treatment which is associated with highly complete stable long term remission rates for patients with generalized myasthenia gravis.

Keywords: Generalized myasthenia gravis, Thymectomy, Complete stable remission rate

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Myasthenia gravis [MG] is an uncommon, organ specific, autoimmune chronic neuromuscular disorder involving the production of autoantibodies directed against the nicotinic acetylcholine receptors (anti-AchRab). The incidence of myasthenia gravis is about 3 to 4 per million per year, and the prevalence is about 60 per million, with higher figures in countries where all modern diagnostic and therapeutic measures are available. It is characterized by weakness and rapid fatigability of voluntary muscles. Ocular muscles are frequently involved, making ptosis and diplopia the most common symptoms at onset[1].

The distribution of myasthenia gravis is age- and sex-related, with an incidence that is twice as high in women than in men. For women, the peak age at onset is in the childbearing years, whereas in men there is no evident peak age[2]. The treatment options that have been demonstrated in symptoms improvement include anticholinesterase drugs, immunosuppressive agents, intravenous immunoglobulin, plasma phreresis, and surgical thymectomy[3]. About 15% to 20% of patients with myasthenia gravis experience MG crisis. The first crisis occurs within the first two years after diagnosis in about 75% of patients. In some patients, MG crisis is the initial presentation of the disease. Patients with MG crisis are typically admitted to an intensive care unit due to acute respiratory failure[4].

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The thymus is known to play an important role in T-lymphocyte education and self-tolerance, and thymus pathology is thought to be an important mediator in the development of myasthenia gravis. The relationship between myasthenia gravis and pathology of the thymus was first recognized in 1901 by Weigert after a thymoma was found in a myasthenia gravis patient[5]. The first thymectomy was performed by Sauerbruch in 1911 for a patient with hyperthyroidism and myasthenia gravis[1]. In 1939, Blalock published a series showing improvement of myasthenia gravis after thymectomy[7]. During the following years, thymectomy gained widespread acceptance as a treatment for myasthenia gravis in comparison with more conservative treatments, such as immunosuppressive therapy and plasmapheresis. Complete stable remission [CSR], as defined by the Myasthenia Gravis Foundation of America [MGFA], is a clear end point for evaluation of treatment results and can minimize inter-observer discrepancies[8]. However, complete stable remission is a time-dependent event, and the results have varied in recent studies from 25% to 58.2%[9-12]. In addition, it is also still unclear as to what prognostic factors can help in predicting the long-term treatment results[13-15]. Therefore, we conducted this retrospective study to clarify the rate of achieving long-term complete stable remission and to identify prognostic factors that are associated with complete stable remission after thymectomy in the treatment of myasthenia gravis.

Materials and Methods

Between January 1993 and December 2013, 330 consecutive generalised myasthenia gravis patients underwent thymectomy in Srinagarind Hospital, administered by the Faculty of Medicine at Khon Kaen University. Of these, 147 patients were excluded from this study due to incomplete data or loss of follow-up. The remaining 183 patients were included in the study; however only 113 patients had more than 10 years of follow-up data that can be analysed for calculating the long-term complete stable remission rate. The preoperative patient profiles, treatments, and post-operative outcomes were retrospectively reviewed from medical records. The preoperative disease severity was evaluated according to the Myasthenia Gravis Foundation of America [MGFA] classification system, i.e.,

Class 1 - ocular muscle weakness only
Class 2 - mild generalized weakness
Class 3 - moderate generalized weakness
Class 4 - severe generalized weakness
Class 5 - intubation required

The indications for thymectomy included;

1) Patients under 60 years old with moderate to severe myasthenia gravis weakness.

2) Patients with mild weakness involving the respiratory (breathing) or oropharyngeal (swallowing) muscles.

3) Patients with myasthenia gravis with a thymoma.

There was no surgery in patient with ocular myasthenia gravis only in this study as recommendation.

The collected clinicopathological parameters were sex, age at onset, age at operation, disease duration, follow-up time, underlying disease, preoperative MGFA classification, medical treatment before surgery, intensive care unit [ICU] stay, pre-operative ventilator support, the length of hospital stay, operative method, post-operative complications, MGFA post-intervention status, complete stable remission rate at 10-year follow-up, time to complete stable remission, surgical morbidity and mortality, and pathologic classification.

Two surgical approaches were practiced in this study.

Extended trans-sternal thymectomy via full median sternotomy is the surgical approach in the majority of cases. For patients with thymic mass, once exploration for metastasis is completed, the tumor is resected en bloc along with the entire thymic tissue. En bloc resection is also performed at any point where adherence or invasion to surrounding structures is found.

Video assisted thoracoscopic [VATS] thymectomy; because of early inexperience, we tried to avoid VATS thymectomy in those cases with thymoma, and all of the cases were unilateral VATS thymectomy using three right-sided ports. The patients were positioned in the semisupine position with right side elevation using roll behind right shoulder, back and hip. Double lumen endotracheal tube with selective left lung ventilation was performed to collapsed right lung. We routinely worked from right to left and inferior to superior. The right pericardial fat pad and pleura along phrenic nerve and the right thymic pole were firstly dissected. After that, the left pleura and the left lower thymic pole were dissected, and right and left cervical poles superior and superficial to left inominate vein were then finally dissected. All patients who underwent VATS thymectomy had a

follow-up time not more than 10 years, so they were included only in the demographic and operative data analysis but are excluded from long-term complete stable remission rate analysis.

Post operative follow-up

The post-operative patients' clinical symptoms were evaluated during the index hospitalisation for thymectomy, and each patient had regular post operative follow-up, which were carried out on at least four times per year. Muscle weakness and the involved sites were carefully examined. The therapeutic response to thymectomy was compared with the patient's preoperative status and assessed according to MGFA post-intervention status.

MGFA post intervention status definition

Complete stable remission was defined as absence of clinical myasthenia gravis during a particular period of time, with the patient not experiencing weakness, nor any muscle-related symptoms for at least one year. The patient also does not require any therapy upon careful examination by a skilled evaluator of neuromuscular diseases; however, isolated weakness on eyelid closure was acceptable.

Pharmacologic remission was the same as for the complete stable remission criteria, except the patient is still taking some therapy for myasthenia gravis but not cholinesterase inhibitor.

Minimal manifestation was defined as the patient had no symptoms but had some weakness on examination for some muscles.

Improve was a substantial decrease in clinical manifestation with reduction in myasthenia gravis medications.

Unchanged was the clinical manifestations and medications needed are still the same as for preoperative status.

Worse was defined as clinical manifestations worsening and more medications needed compared with preoperative status.

Statistical analysis

Data were collected and analysed retrospectively. The primary endpoint was complete stable remission rate at 10 year. The secondary end points were the prognostic factors for remission. Categorical variables were summarised as frequency (%), and continuous variables were expressed as mean $\pm$ SD. The prognostic factors were assessed using multiple logistic regression analysis, and *p*-values less than 0.05 were considered statistically significant. SPSS version 16.0 was used to perform data analysis.

Results 183 myasthenia gravis patients were enrolled in this study. The majority of patients were women, in 141 cases (77%). The median age at onset was 32.91 years (range 11 to 70 years). The median follow-up time was 123.51 months (range 26 to 216 months), and the median preoperative disease duration was 23.67 months (range 2 to 204 months). Of these, 114 patients (62.3%) were corticosteroids dependent before surgery, 24 patients (13.1%) had thymoma, and 18 patients (9.7%) had underlying hyperthyroidism preoperatively. According to MGFA classification; 129 patients (70.5%) were MGFA Class II, as shown in Table 1.

Regarding the operative data, 173 cases (94.5%) underwent extended trans-sternal thymectomy, whereas VATS thymectomy was performed in 10 cases (5.5%). Postoperative complications occurred in 26

Table 1. Demographic data

	n = 183
Gender	
Male	42 (23%)
Female	141 (77%)
Age (years)	11 to 70
Range (mean)	(32.9)
MG-age at onset	
≤40 years	131 (71.6%)
>40 years	52 (28.4%)
MG-age at operation	
≤45 years	147 (80.3%)
>45 years	36 (19.7%)
Disease duration (months)	2 to 204
Range (mean)	(23.7)
Pre-op. MGFA clinical classification	
Class 1-ocular muscle weakness only	0
Class 2-mild generalized weakness	129 (70.5%)
Class 3-moderate generalized weakness	36 (19.6%)
Class 4-severe generalized weakness	11 (6.0%)
Class 5-intubation required	7 (3.8%)
Thymoma	
With thymoma	24 (13.1%)
Without thymoma	159 (86.9%)
Follow-up times (months)	26 to 216
Range (mean)	(123.5)
Corticosteroid used	
With corticosteroid	114 (62.3%)
Without corticosteroid	69 (37.7%)
Hyperthyroidism	18 (9.7%)
Pre-operative ventilator	4 (2.2%)

cases (13.7%). Of these, 22 patients (11.7%) developed pneumonia, which is the most common complication. One patient developed post-operative MG crisis that needed prolong endotracheal intubation and also prolonged length of ICU stay up to 50 days and length of hospital stay up to 150 days, postoperatively. The mean length of ICU stay was 2.23 days (1 to 50), and the mean length of hospital stay was 9.69 days (range 4 to 150). There was no peri-operative mortality. Thymic hyperplasia was the most common thymic pathology that was presented, in 114 cases (62.3%), and thymoma was seen in 25 cases (13.7%). Regarding postoperative MGFA status, 87 cases (47.5%) were in complete remission, 57 cases (31.1%) were in improvement, 22 cases (12%) had minimal manifestation, and 10 cases (5.5%) were not changed. However, 3 cases (1.6%) had worse clinical outcome due to poor preoperative status, such as pre-operative and post-operative myasthenia gravis crisis, and some had very long disease duration before surgery, as depicted in Table 2.

Of the 113 patients with follow-up time longer than 10 years, long-term complete stable remission was achieved in 58 cases (51.3%), and mean duration to complete stable remission was 21.6 months (Range 2 to 94 months).

The possible prognostic factors for myasthenia gravis patients who underwent thymectomy were analysed. Those potentially prognostic factors affecting outcome were estimated using univariate and multivariate analysis. Univariate analysis showed that patients with an MG-age at onset of less than 40 years old and MG-age at operation less than 45 years old including the MGFA classification were associated with a significantly higher probability of achieving complete stable remission. On the other hand, we found that corticosteroid therapy was a worse prognosis factor for achieving complete stable remission, as shown in Table 3.

However, further analysis was performed of these significant prognostic factors using multivariate analysis, the results showed that there were no significant prognostic factors associated with complete stable remission. However an MG-onset age of less than 40 years old seems to be the most strongest prognostic factor associated with complete stable remission, even though it had no statistical significance in our study, as shown in Table 4.

Table 2. Operative data

	n = 183
Type of operation	
Extended trans-sternal thymectomy	173 (94.5%)
VATS thymectomy	10 (5.5%)
Length of ICU stay (days)	1 to 50
Range (mean)	(2.23)
Length of hospital stay (days)	4 to 150
Range (mean)	(9.69)
Post operative complications	
Pneumonia	25 (13.7%)
Pneumothorax	22 (11.7%)
MG crisis	3 (1.5%)
Bleeding	1 (0.5%)
Superficial or deep wound infection	0
Recurrent laryngeal nerve palsy	0
Thymic pathology	
Thymoma	25 (13.7%)
Thymic hyperplasia	114 (62.3%)
Lymphoid hyperplasia	15 (8.2%)
Other	29 (15.8%)
MGFA post operative clinical status	
Complete remission	87 (47.5%)
Pharmacological remission	0
Minimal manifestration	22 (12%)
Improvement	57 (31.1%)
Unchanged	10 (5.5%)
Worse	3 (1.6%)
Mortality rate	0%

Discussion

Thymectomy is an established therapeutic modality for the treatment of myasthenia gravis that can result in both improvement of symptoms and complete remission. The method used to assess the results of thymectomy is critical when attempting to evaluate the procedure's efficacy. It is difficult to compare reported outcomes regarding the use of

Table 3. Univariate analysis of prognostic factors associated with complete stable remission

	Odds ratio	95% CI	*p*-value
MG-age at onset <40 years	4.6	1.7 to 12.3	0.002
MG-age at operation <45 years	6.7	1.7 to 25.1	0.005
Male gender	1.3	0.5 to 3.4	0.518
MGFA classification	1.7	1.0 to 2.8	0.033
Corticosteroid therapy	0.5	0.2 to 1.1	0.079
Thymic pathology	1.5	0.9 to 2.2	0.104
Thymoma	0.6	0.1 to 2.8	0.514
Disease duration <2 years	1.0	0.9 to 1.0	0.517

Table 4. Multivariate analysis of prognostic factors influence complete stable remission after thymectomy

	Odds ratio	95% CI	*p*-value
MG-age at onset <40 years	3.1	0.9 to 10.1	0.058
MG-age at operation <45 years	2.4	0.5 to 12.0	0.269
MGFA classification	1.5	0.9 to 2.6	0.118
Steroid therapy	0.6	0.3 to 1.4	0.245

thymectomy in cases of myasthenia gravis, as the end point is vague and multifarious. The primary end point of our study was complete stable remission rate as defined by the MGFA since it has a straightforward definition so that the use of complete stable remission as an end point can minimize inter-observer discrepancies. The general trend which emerged was that the longer the follow-up after thymectomy, the better the results tended to be. The results of our study showed that the complete stable remission rate was 51.3% at 10 years, which was similar to those found in previous studies. The existing data seem to support an extended resection that removes as much thymic tissue as possible to achieve a higher complete stable remission rate. Masaoka et al[10] used extended trans-sternal thymectomy in cases of non-thymomatous MG and showed remission rates to be 45.8% at 5 years, 55.7% at 10 years, and 67% at 15 years. El-Medany et al used the maximal thymectomy and showed complete stable remission rates of 37.4% at 3 years, 58.2% at 10 years, and 75% at 15 years[11]. Diaz A et al performed a meta-analysis of 137 studies about thymectomy in myasthenia gravis and found that the complete stable remission rate in patients who received thymectomy was 54%, which was higher than in those patients who received medication alone, which reported a complete remission rate of about 38% at 10 years[12]. Venuta F et al also reported their results of thymectomy with a mean follow-up of 119 months; 71% of all patients improved their clinical status, 25% without medications and asymptomatic; 46% with a reduction of medications and/or clinically improved; 39 (18%) had a stable disease with no clinical modifications; and 12 (5%) presented a deterioration of their clinical status with worse symptoms, required more medications, or both[13]. This study also analysed the prognostic factors that may be associated with complete stable remission and reported that the age at onset of the disease of less than 40 years old, age at operation of less than 45 years old, and the MGFA classification were the significant favourable prognostic factors, whereas the use of corticosteroid therapy was a significant unfavourable prognostic factor according to univariate analysis. However, when evaluated using multivariate analysis, the results demonstrated that none of these prognostic factors were significant factors, and that only the MG-age at onset of less than 40 years old seems to be the strongest prognostic factor associated with complete stable remission. These results were similar to the results of previous studies. Masaoka also reported the prognostic factors and found that age at onset of less than 34 years ($p<0.05$) and shorter duration of symptoms of less than 2 years ($p<0.05$) were favorable prognostic factors[13]. Park IK et al also reported that early onset (age at onset of less than 40 years) was a good prognostic factor, while steroid therapy was a poor prognostic factor[14]. Perrot DM et al reported that postoperative improvement was significantly greater in patients with advanced MG (stages IIB, III and IV), whereas a higher rate of remission occurred in patients with mild MG (stages I and IIA), and in those with thymic hyperplasia[15]. Tansel T et al also reported that overall age at onset of less than 45 years showed a higher probability of achieving complete stable remission during follow-up (81% benefit rate [BR], $p<0.02$)[16]. Furthermore, Lin M et al analyzed the prognostic factors and showed that three prognostic factors that were associated with better remission rates were hyperthyroidism, age at onset of less than 40 years, and the presence of thymic hyperplasia pathology. Finally, Andres Diaz et al also analysed the prognostic factors in their meta-analysis on the outcome after thymectomy in myasthenia gravis and found that thymic hyperplasia pathological subtype and age at onset of less than 45 years were good prognostic factors for complete stable remission. The reasons why our results regarding the prognostic factors associated with complete stable remission were not significant on multivariate analysis may be due to the small sample size in this study, and not all of our patients had follow-up of more than 10 years that was long enough to evaluate long-term outcome. We could not analyse the long-term results of VATS thymectomy in our center due to the fact we only recently started this operation, so VATS thymectomy is quite early in terms of experience and only a small percentage of patients have undergone this kind of operation.

Study limitations

The present study has some limitations. It was a retrospective study review and quite small in sample size due to about one third of patients who had undergone thymectomy being excluded from the study due to there being loss or incomplete follow-up, and some patients had incomplete data. In addition, for the studied population, 70 patients could not used for analysis of long-term outcome because their follow-up period was less than 10 years. However, our study is still comparable to other studies with smaller sample sizes.

Conclusion

Extended trans-sternal thymectomy is safe and the most beneficial procedure for treatment of myasthenia gravis patients. Thus, thymectomy should be considered as an option in treatment of myasthenia gravis patients to increase the chance of long-term remission or improvement. Young age at presentation, particularly those patients who are less than 40 years old, tend to have a good prognosis, while long term steroid use may be the worse prognostic factor.

What is already known on this topic?

Thymectomy is an established therapeutic modality for the treatment of myasthenia gravis that can result in both improvement of symptoms and long term complete remission. Trans-sternal thymectomy is an established standard surgical approach with the best complete stable remission rate benefit, and this result is enhanced over long-term follow-up.

What this study adds?

Our results showed the same complete stable remission rate to previous studies. However, in terms of prognostic factors analysis, we found that only an MG-onset age of less of than 40 years old seems to be the strongest prognostic factor associated with complete stable remission rate according to multivariate analysis, even if it was not statistically significant.

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Potential conflicts of interest

The authors declare no conflicts of interest.

References

1. Pascuzzi RM. The history of myasthenia gravis. Neurol Clin 1994;12:231-42.
2. Walker MB. Case showing the effect of prostigmin on myasthenia gravis. Proc R Soc Med 1935;28: 759-61.
3. Mineo TC, Pompeo E. Extended videothoracoscopic thymectomy in nonthymomatous myasthenia gravis. Thorac Surg Clin 2010;20:253-63.
4. Oosterhuis HJ. The natural course of myasthenia gravis: a long term follow up study. J Neurol Neurosurg Psychiatry 1989;52:1121-7.
5. Weigert C. Pathologisch-anatomischer Beitrag zur Erb□-schen Krankheit (Myasthenia gravis). Neurol Centralbl 1901;20:597-601.
6. Kirschner PA. Alfred Blalock and thymectomy for myasthenia gravis. Ann Thorac Surg 1987;43:348-9.
7. Jaretzki A, III, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, et al. Myasthenia gravis: recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Neurology 2000;55:16-23.
8. Masaoka A, Yamakawa Y, Niwa H, Fukai I, Kondo S, Kobayashi M, et al. Extended thymectomy for myasthenia gravis patients: a 20-year review. Ann Thorac Surg 1996;62:853-9.
9. El Medany Y, Hajjar W, Essa M, Al Kattan K, Hariri Z, Ashour M. Predictors of outcome for myasthenia gravis after thymectomy. Asian Cardiovasc Thorac Ann 2003;11:323-7.
10. Diaz A, Black E, Dunning J. Is thymectomy in non-thymomatous myasthenia gravis of any benefit? Interact Cardiovasc Thorac Surg 2014;18:381-9.
11. Venuta F, Rendina EA, De Giacomo T, Della RG, Antonini G, Ciccone AM, et al. Thymectomy for myasthenia gravis: a 27-year experience. Eur J Cardiothorac Surg 1999;15:621-4.
12. Park IK, Choi SS, Lee JG, Kim DJ, Chung KY. Complete stable remission after extended transsternal thymectomy in myasthenia gravis. Eur J Cardiothorac Surg 2006;30:525-8.
13. de Perrot M, Licker M, Spiliopoulos A. Factors influencing improvement and remission rates after thymectomy for myasthenia gravis. Respiration 2001;68:601-5.

14. Tansel T, Onursal E, Barlas S, Tireli E, Alpagut U. Results of surgical treatment for nonthymomatous myasthenia gravis. Surg Today 2003;33:666-70.
15. Lin MW, Chang YL, Huang PM, Lee YC. Thymectomy for non-thymomatous myasthenia gravis: a comparison of surgical methods and analysis of prognostic factors. Eur J Cardiothorac Surg 2010;37:7-12.