Factors predicting surgical outcome of thymectomy in myasthenia gravis: A 16-year experience

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Abstract

Aim: To assess the surgical outcome of myasthenia gravis (MG) following thymectomy and to determine the outcome predictors to such therapeutic approach. **Materials and Methods:** This study is a retrospective review of 80 consecutive thymectomies performed for MG over a 16-year period. **Results:** There were 41 females and 39 males (mean age, 34.32 years) with mean disease duration of 17.45 months prior to surgery. Stagewise distribution of the patients revealed 2.5% in stage I, 48.7% in stage IIA, 33.8% in stage IIB, 8.7% in stage III, and 6.3% in stage IV. The surgical approach was either trans-sternal (n=67) or video-assisted thoracoscopic route (n=13). Follow-up was obtained in 91.2% (n=73) of patients with mean duration of 67.7 months. At their last follow-up, 26.0% were in complete remission, 35.6% were asymptomatic on decreased medications, and 17.8% had clinical improvement on decreased medications. Overall, 79.4% of patients benefited from surgery, 8.2% had unchanged disease status, and 12.3% worsened clinically. Factors influencing favorable outcome include sex, disease stage, gland weight, and preoperative medication with anti-cholinesterase (P<0.05). There was one death in the perioperative period due to septicemia. Two patients died at fourth and seventh month following thymectomy. **Conclusion:** Thymectomy for MG is safe and effective. Certain influencing factors may shape treatment decisions and target higher risk patients.

Key Words

Myasthenia gravis, thymectomy, video-assisted thymectomy

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Introduction

Myasthenia gravis (MG) is one of those curious diseases whose pathophysiology continues to be elucidated. Treatment, now available, is highly effective, although a specific cure remains elusive. The controversies in the treatment of MG are two:

1. On which patients should thymectomy be performed and
2. Should the approach be radical trans-sternal or increasingly, thoracoscopic and radical mediastinal dissection or transcervical.

Currently, the indications for thymectomy in MG include early, generalized, moderate to severe disease stabilized with medication, and resistant ocular disease.[1,2] These indications are based on circumstantial evidences and expert opinion.

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The main focus of the current studies has been to determine predictors of response in order to maximize benefit through careful patient selection. In similar vein, we reviewed our institutional experience with operative thymectomy in 80 patients with MG, to critically review surgical outcome, identify predictors of response, and identify those patients most likely to benefit from the procedure.

Materials and Methods

A retrospective study of the patients undergoing thymectomy for MG during the last 16 years (1991–2007) was performed. After the study design, a performa was prepared. Information was filled in the performa based on the data collected from hospital case records; follow-up register, e-mail, and telephonic communication with patients, relatives, and their attending physicians. The medical records were reviewed for demographics, preoperative symptoms, stage of disease, surgical approach, postoperative complications, and surgical outcome. Five different consultants in the department performed surgery. The diagnosis of MG was based on: (1) typical history, (2) physical findings, (3) positive decremental response to repetitive nerve stimulation, (4) high acetylcholine receptor antibodies titers (whenever possible),

and (5) a positive neostigmine test. Chest X-ray and CT scan thorax were done to confirm or exclude the presence of thymoma. Thymectomy was carried in patients who were (1) less than 70 years of age, (2) had generalized symptoms of MG, (3) ocular symptoms refractory to medical treatment, or (4) thymoma. A uniform protocol of perioperative care was followed, including preoperative preparation, anesthetic and operative technique, postoperative medical, and nursing care. Plasmapheresis or intravenous immunoglobulin was used preoperatively in selected group of patients with severe bulbar symptoms or respiratory muscle weakness. Patients who were on steroids prior to surgery were covered with perioperative stress doses and later weaned off slowly. The preoperative severity of the disease was classified according to the Osserman and Jenkins 1971 criteria.[3] Postoperatively, all patients were started on anticholinesterase or steroids, doses of which were gradually reduced depending on the myasthenic symptoms. Measurement of postsurgical clinical outcome of the patient was done according to the DeFilippi classification [4] as follows:

Class I: Complete remission; no medications
Class 2: Asymptomatic; on decreased medication
Class 3: Improvement in symptoms; on decreased medications
Class 4: No change in symptoms or medications
Class 5: Worsening symptoms

The outcomes were noted at every point of follow-up and were ultimately categorized according to patient condition at the last known point of follow-up. The minimum time of follow-up was 2 months. The same operating surgeon and the neurologist together followed up all the patients. Video-assisted thymectomy (VATS) was introduced in the year 1999 using the right-sided thoracoscopic approach. Trans-sternal total thymectomy was performed through a standard median sternotomy. In both the approaches, maximal thymectomy was performed. The extent of resection was superiorly up to the lower pole of thyroid, inferiorly the diaphragm, and laterally the phrenic nerves, to remove all the perithymic fat of the anterior mediastinum and aorto-pulmonary window [Figure 1]. Parts of mediastinal pleura or pericardium were also removed in the presence of infiltrating tumor. The patients were extubated as early as possible in the postoperative intensive care unit. Postoperative complications included all

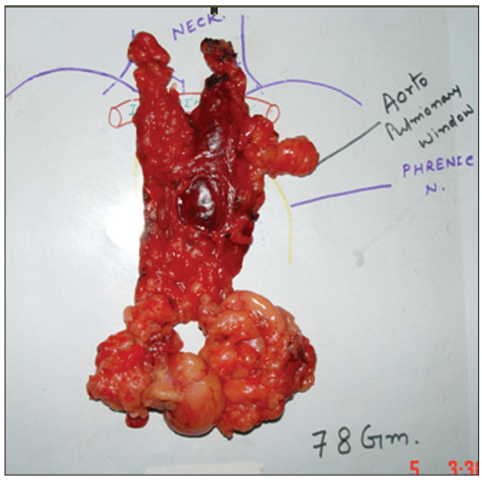

Figure 1: Extent of resection in "maximal" thymectomy

events occurring within 30 days of surgery. Statistical analysis was performed using SPSS version 14.0. Student's *t*-test and chi-square test were used for determination of statistical significance (P <0.05).

Results

Eighty patients underwent thymectomy during the study period. There were 39 males and 41 females. The mean age of the patient at disease onset was 34.32 years (range 10 to 65 years). The mean duration of symptoms was 17.45 months (range 10 days to 132 months). Majority (90%) of the patients presented with combination of symptoms, in which generalized fluctuating weakness of different severity was the most dominant one. Two (2.5%) patients had pure ocular disease, while seven (8.75%) had dominant bulbar symptoms. Two (2.5%) patients were in stage I, 39 patients (48.7%) in stage IIA, 27 (33.8%) in stage IIB, 7 (8.7%) in stage III, and five (6.3%) in stage IV. There was no significant difference between male and female patients in their mean age at the time of surgery, mean duration of symptoms, or in the Osserman's class of the disease. Acetylcholine receptor antibody (ACh-R) titers were available in 25 patients only. A significant proportion of patients could not undergo ACh-R antibody estimation because of financial constraints. Four (16%) patients had negative Ach-R antibody titer and 21 (84%) had positive titers. CT scan thorax was available in only 53 patients. Twenty-two patients (41.5%) had normal scan findings, 7 (13.3%) had enlarged thymus, 23 (43.4%) had thymoma, and 1 (1.8%) had thymic cyst. A detailed account of all drugs and other medical treatment was available in 71 patients. Forty-one of 71 patients were on anticholinesterase agents alone, 24 were on anticholinesterase, steroids, and the remaining 6 on combined treatments including anticholinesterase, steroids, azathioprine, and/or cyclophosphamide. The mean duration of medical treatment was 16.94 months (range, 10 days to 132 months). Sixty-seven (83.75%) patients underwent thymectomy through a trans-sternal approach, while 13 (16.25%) had VATS. Postoperative complications occurred in 23 patients—chest infection in 5 patients, respiratory failure in 3 patients, phrenic nerve palsy in 1 patient, sternal wound dehiscence in 1 patient, pericardial effusion in 2 patients, mediastinal collection in 6 patients, cholinergic crisis in 4 patients, and mediastinal bleed in 1 patient. Ten of 23 patients had major postoperative complications and one died of septicemia resulting from sternal dehiscence leading to mediastinitis. Three patients required additional procedures: Tracheostomy in one (for prolonged ventilator support), the second required pericardiocentesis for cardiac tamponade, and the third underwent reexploration for mediastinal bleeding. Phrenic nerve palsy occurred in one patient who had thymoma invading the nerve. Histopathological diagnosis was available in 79 patients, of which —27 (34.2%) had thymoma, —32 (40.5%) had thymic hyperplasia, normal thymus in 13 (16.5%), involuted thymus in 2 (2.5%), thymic cysts in 3 (3.7%), and unremarkable thymus in 2 patients (2.6%). The mean weight of the thymus gland (n=75) was 33.42g (range 3–138g). Under the age of 40, 50% patients had thymic hyperplasia, while 25% patients had thymoma, whereas in a group above age 40, 17.4% of patients had thymic hyperplasia and 56.5% had thymoma (P=0.022). Follow-up was obtained in 91.3% (73 of 80) of patients. The mean duration of follow-up was 67.75 months (range, 2–159 months). Two

patients died in the follow-up, one at an interval of 7 months and the other 4 months later. Seven patients lost to follow-up. The cause of death in both patients was exacerbation of MG and respiratory failure due to severe chest infection. One of these patients had invasive thymoma type B2.

Surgical outcome

The data on clinical response to thymectomy were available in 73 patients at the last follow-up. According to DeFilippi criteria, 19 patients (26.0%) were in complete remission (class I), 26 patients (35.6%) were asymptomatic (class II), and 13 patients (17.8%) had clinical improvement (class III). Thus, the overall percentage of patients benefiting from thymectomy was 79.4%. In six patients (8.2%), disease remained unchanged (class IV) and in nine patients (12.3%) the symptom worsened (class V).

Predictors of outcome

Among the patients who achieved complete remission, there were 12 females (31.6%) and 7 males (20%). Six (17.1%) male patients had deterioration in comparison to three (7.9%) female patients ($P<0.05$).

Fifteen patients (28.8%) under the age of 40 achieved complete remission in comparison to four (19.0%) beyond the age of 40. The mean age of patients achieving complete response was 30.11 years (range, 13–62 years) and 37.17 years for those who did not have complete response ($P=0.73$).

Among the patients with disease of less than 1 year duration, 14 patients (28.6%) achieved complete response in comparison to 5 (20.8%) who were having disease duration of more than 1 year ($P=0.24$).

Stagewise response status [Table 1] was as follows: 1 patient (50%) in stage I, 11 patients (29.7%) in stage IIA and 7 (30.4%) in stage IIB achieved complete clinical response. No patients in stage III and IV achieved complete response. Patients in stage IIA and IIB were most likely to reach the complete clinical response ($P=0.05$). In addition, 28.6% patients in stage III and 50% patients in stage IV had worse prognosis, in comparison to 2.7% patients in stage IIA and 17.4% patients in stage IIB.

When the details of medication given in the preoperative period were studied, it was observed that 11 of 41 patients (26.8%) who were solely on anticholinesterase agents (pyridostigmine and prostigmine) achieved complete response in comparison to 6 of 24 patients (25%) with anticholinesterase plus steroids and 2 of 6 patients (33.3%) with anticholinesterase plus steroids and azathioprine. On the contrary, 3 of 6 patients (50%) who were taking anticholinesterase plus steroids and azathioprine had worse prognosis in comparison to 3 of 41 patients (7.3%) with anticholinesterase agents only and 3 of 24 patients (12.5%) with anticholinesterase plus steroids ($P<0.01$).

Table 1: Osserman stage and thymectomy outcome in myasthenia gravis

Stage	Patients no.	Response status (%) DeFillipi classification				
		Class 1	Class 2	Class 3	Class 4	Class 5
I	2	50	0	50	0	0
IIA	37	29.7	32.4	27.0	8.1	2.7
IIB	23	30.4	43.5	4.3	4.3	17.4
III	7	0	57.1	0	14.3	28.6
IV	4	0	0	25.0	25.0	50.0

The duration of medical treatment received by the patients prior to surgery had no statistical correlation with the outcome. Among the patients who were treated for less than 1 year, 13 of 47 patients (27.7%) achieved complete response, in comparison to 5 of 23 patients (21.7%) who received treatment for more than 1 year ($P=0.17$).

Patients with positive acetylcholine receptor antibody titer ($n=21$) had better outcome (7 of 21 patients) than patients with negative acetylcholine receptor antibody titers (nil out of 4 patients). However, this difference did not reach statistical significance because of small sample size ($P=0.11$).

Patients who underwent surgery through video-assisted approach had better clinical outcome than patients who underwent trans-sternal approach (30.8% and 25.0%, respectively) ($P=0.53$).

When the histopathology and clinical outcome was correlated, it was observed that 10 patients (33.3%) with hyperplastic glands achieved complete remission when compared with 2 patients (8.7%) with thymoma, 4 (33.3%) with normal gland, 1 (50%) with involuted thymus, and 2 (66.7%) with thymic cyst ($P=0.11$). Failure to identify a relationship between pathologic parameters and clinical outcome may result from a lack of statistical power secondary to the large number of pathologic subsets relative to patient numbers.

Fourteen patients (35.9%) with gland weight up to or less than 30 g achieved complete response in comparison to 5 (15.6%) patients with gland weight more than 30 g. In the group of patients who had worsening of symptoms, 21.9% of patients with specimen weight more than 30 g had deterioration in comparison to 2.6% of patients with weight less than 30 g ($P<0.05$).

Discussion

Thymectomy is potentially beneficial in all patients of autoimmune MG with life expectancy of more than 10 years or in whom a thymoma is suspected. It has now become a standard policy to offer thymectomy to all patients between the ages of puberty and at least 55 years with generalized MG and to a select group of patients with ocular MG. Despite this fact, a 16-month lag between the diagnosis of MG and surgical treatment was seen in our study, which is consistent with other studies.[5,6] It remains unclear whether this delay in surgical treatment represents reluctance on the part of patients or their physicians to exercise the option of surgery. Economic and logistic difficulties and limited insight into the disease often interfere with early delivery of optimal care in India and other developing countries.

We considered complete stable clinical response the best measure for comparison with other reported series but had difficulties making exact comparison because of the lack of objective definitions of severity of the illness, variable patient's

selection, timing of surgery, type of surgery, and methods of result analysis and outcome assessments in the different series. The overall improvement rate (79.4%) in our study was comparable to other large studies [Table 2]. However, the complete stable response rate (26.0%) was less in comparison to other reported series (14%–47%).[5,6-12] The inconsistencies across the studies and the difficulty in directly comparing results are universally acknowledged and the same has been addressed by the Myasthenia Gravis Foundation of America (MGFA) task force.[13] In addition, it has also been observed that postoperative remission from MG is usually not apparent until after 1 year and the full effect is not felt for 5 years,[6,7] because, the primed B-cell and helper T-cells theoretically remain in circulation for prolonged period even after removal of the source of autoimmunization (thymectomy). This delay might have reduced our rate of observed remission. Complete remission in our study was achieved in patients at an average of 71.16 months postoperatively, which is longer than our average follow-up of 67.7 months. Therefore, if longer follow-up had been done, we could have expected an increase in our rate of complete remission.

A male:female ratio of only 1:1.1 was noted in this review, which is quite different to the majority of previously published studies showing a preponderance of female patients.[5] In general, female patients tend to respond to treatment better than their male counterparts.[14,15] Our study also shows statistically significant associations between female sex and the outcome.

Age-related outcome in our study is comparable with some other studies where age less than versus more than 40 years was considered.[15] Budde *et al*.[8] have shown strong correlation between age and outcome, 81% response rate for 50 years of age or younger and 55% for older than 50.

As observed by others,[16] we also found that duration of the disease (<1 and >1 year) did not correlate significantly with the outcome.

It has been reported that patients in Osserman stage I and stage III have higher complete clinical response rate,[14] but we found a higher complete stable response rate in stage I and stage II disease which is consistent with other studies.[17,18] Hassan *et al*.[19] have shown better symptomatic improvement with more advanced stages. On the contrary, we had negligible complete response for patients in stage III and stage IV. In general, the patients with mere ocular symptoms, or those whose condition is well controlled with acceptable medical treatment, are usually not first-line candidates for thymectomy. On the other hand, Shrager *et al*.[20] reported a complete remission in 50% of pure ocular MG. They also noted as many as 50% of pure ocular MG patients historically deteriorate or develop generalized MG. In their pure ocular myasthenic group of patients who had undergone thymectomy, the incidence of MG progression was zero. Some authors have reported remission rate of 60% in purely ocular disease and so recommend thymectomy for Osserman I MG.[21] We had only two patients in this group and observed complete response in one patient. Taking into account the response in one patient, it will be a premature comment on the issue of recommending surgery in patients with purely ocular disease. However, based on the collective experience from different series, it is believed that thymectomy should be tried in all patients with ocular involvement, because two-third of them develops generalized disease in due course of time.[17]

AChR antibody was detected in 84% patients, similar to other reported series (75%–85%).[22,23] In our study, favorable response was observed in seropositive patients in comparison to seronegative patients although it did not reach statistically significant proportions unlike others.[5] Jaretzeki *et al*.[24] have shown no obvious relationship between seropositive and seronegative patients.

As expected, patients who received immunosuppressive agents preoperatively had significant deterioration than those patients who received only cholinesterase inhibitors (P<0.01).

On analysis of the surgical technique (VATS vs. trans-sternal approach), patients who underwent video-assisted thoracoscopic thymectomy had better clinical response in comparison to trans-sternal approach, but the difference was not statistically significant. Many others have also reported similar results.[25] The better response rate in the VATS group may be due to a failure to include patients with thymoma and patients with severe respiratory complications.

It has been reported in various series that thymic hyperplasia carries the highest chance of complete clinical response and best prognosis, whereas the thymoma carries the lowest response rate and the worst prognosis.[6,26] However, we did not make any such observation. However, the presence of thymoma has often been found to correlate with poorer response to thymectomy. [7,10,15] In our study, 33.3% of patients with hyperplastic thymus glands achieved complete remission in comparison to 8.7% with thymoma, but the difference was

Table 2: Comparison of outcome of thymectomy in various series

Authors/year	Patients no.	Follow-up (month)	Complete remission (%)	Overall improvement (%)
Bril *et al*., 1998[7]	52	100	44.2	–
Mineo *et al*., 2000 [25]	31	48	36	96
Budde *et al*., 2001[8]	113	51	21	75
Yim *et al*., 2002[9]	36	41	13.9	87.8
Zielinski *et al*., 2004[6]	48	12	18.8	83.3
Glinjongol *et al*., 2004[10]	30	41.80	40	80
Manlulu *et al*.,2005[11]	38	69	22.2	91.6
Huang *et al*., 2006[12]	168	98.9	30.5	88.3
Present study	80	67.75	26	79.4

not significant. Interestingly, 30.4% patients with thymoma symptomatically worsened in comparison to 3.3% patients with hyperplastic gland. Jaretzki and coworkers [24] found a decreased remission rate and increased mortality among thymomatous patients with MG. However, this trend was not seen in our study.

We found significantly worse outcome in patients whose resected specimen weight measured more than 30 g irrespective of the pathology. We did not find any such comparative analysis taking gland weight as one of variable in study of outcome.

Thus, our results clearly indicate that age, pathological subtypes, duration of symptoms or medication, type of surgical procedure, and acetylcholine receptor antibody titer do not seem to significantly alter or influence the outcome. However, female sex, early stage, preoperative medication, and gland weight are the positive predictor of clinical outcome.

Conclusions

Thymectomy deserves consideration as the first option until more effective treatment for MG become available. Female sex, early osserman stage, disease stabilized on anticholinesterse medication, and gland weight are the potential predictors of surgical outcome for MG. However, these factors should not serve to absolutely indicate or contraindicate the procedure for certain candidates, but rather should assist in decision making and targeting high-risk patients. Remission failure in advanced stage underlines the importance of early recognition and referral. In our institute, neurologists are well aware of this fact and support the view of early referral except for perhaps the occasional patients with Osserman 1, purely ocular myasthenia that had not progressed in 2 years and was therefore unlikely to progress. The message about impressive surgical outcome, operative safety, waxing, and waning nature of the disease needs to be transferred to the patients and general population of clinicians who are not strong practitioner in the art of treating MG.

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