Thymectomy in Myasthenia Gravis at Hospital Universiti Sains Malaysia: A 10 Years Review

Running title: Thymectomy in Myasthenia Gravis

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Abstract

Background: Thymectomy is considered effective treatment modalities for patients with myasthenia gravis (MG). Although few studies have been reported concerning thymectomy in MG in Asians countries, there is no published data about thymectomy in MG in Malaysia. We aimed to describe the clinical outcome and factors affecting the outcome following thymectomy in MG.

Methods: This was a retrospective study involving 16 patients with MG underwent thymectomy at Hospital Universiti Sains Malaysia commencing from January 2002 till December 2012 with a period of follow-up ranging from 3-120 months.

Results: A total of 16 patients with age of patients ranged between 22-78 years were analysed. Males were the predominant group. The overall remission/improvements rates were 87.5% and clinical unchanged/worsening rates were 12.5%. Thymomamatous or non-thymomamatous MG, histology features, Osserman stage and duration of follow-up were not found to be significant prognostic factor. Postoperative mortality was 6.2% (1 of 16 patients died of septicemic shock).

Conclusion: Thymectomy perhaps provides effective mode of treatment with lower surgical morbidity observed. Patients with lower Osserman stage and both group (patients with thymoma or without thymoma) showed favorable results.
Introduction

Myasthenia Gravis (MG) is an autoimmune disease with a wide range of clinical symptoms, ranging from mild weakness to severe debilitating respiratory failure. It is caused by impaired neuromuscular transmission due to antibodies present at the neuromuscular junction (1). Thymectomy with combination of corticosteroids, immunosuppressive and anticholinesterase agents have been proved to be an effective treatment for MG. Better results have been seen compared to those who are under medical treatment only (2). There is currently limited data regarding thymectomy in MG patients in Malaysia with regards to surgical and non-surgical treatment. Thus, our study was aimed to describe the clinical outcomes following thymectomy for MG in a series of 16 patients and the factors associated with the postoperative outcome.

Patients and Methods

We have done a retrospective study to review the clinical outcomes of 16 patients who had undergone extended thymectomy for Myasthenia Gravis (MG) at Hospital Universiti Sains Malaysia from January 2002 until December 2012 (Table 1). The follow-up period ranging from 3 months to 10 years.

Patients who were included into our study fulfilled the following criteria:

- a) Patient with thymoma and without thymoma (based on Computed Tomography findings).
- b) Patient with severe and generalised MG.
- c) Patient with long-standing duration of MG and symptoms not controlled with oral medication.

Patients were excluded if the thymectomy done for other reasons (e.g mediastinal mass, abscess).

Each patient was evaluated by neurologist and cardiothoracic surgeon prior to surgical intervention. Osserman classification was used for staging: grade I: oculomotor myasthenia; grade IIa: mild generalised MG; grade IIb: moderately severe MG with bulbar involvements, grade III: acute fulminating myasthenia with respiratory crises and grade IV: late severe myasthenia. All 16 patients had undergone extended thymectomy through median sternotomy. Clinical outcome evaluated based on the patient’s symptoms and changes in medication. It further classified according to remission: patient is asymptomatic with no medication required, improvement: improvement of symptoms with reduced medications, unchanged: no change in symptoms and medications and worsening: worsening of symptoms and increase in medications requirement.

The data was analysed using the Statistical Package for Social Sciences version 20.0 (SPSS Inc, Chicago, USA). Results were presented using frequencies and percentages. Median and interquartile range (IQR) were used for descriptive statistics. Non-parametric Fisher’s exact test, and Mann Whitney test were used to compare the outcomes between the remission/improvements group and no change/worse groups with regard to the histology of resected thymus gland, Ossermann classification and follow-up time. For all analyses, the level of statistical significance was defined as p value <0.05.

Results
Majority of patients with MG in this study had limb weakness (87.5%) and ptosis (81.3%) as the clinical symptoms during their early presentation to medical practitioner. Others were dysphagia (75%), diplopia (43.8%), respiratory crises (25%), dysphonia (18.8%) and chest pain (6.3%) (Table 2).

Ten patients were male (63%) and 6 patients were female (37%). Majority was Malay population (81%) and others were Chinese (19%). We did not find any Indian, Siamese or other races in this study. Mean age at disease onset was 35.7 ± 3.9 years (range 18.0-74.0) with a median duration of symptoms to time of operation of 10.0 months (range 3.0 to 120). The mean age of patients was 42 ± 14 years, with a range of 22 to 78 years. The median length of follow-up was 33.8 ± 8.7 months. There is no significant difference in median follow-up between remission and improvement group with unchanged or worst group (p: 0.112) (Table 3).

Histopathologic study of resected thymus gland revealed thymus hyperplasia in 12 cases (75%), thymoma in 3 cases (18.7%) and normal thymic tissue in one case (6.3%) (Figure 2). Although 11 patients (78.6%) with thymus hyperplasia and all patients with thymoma (21.4%) have shown remission and improvement, no statistical correlation could be identified between histopathologic findings with the clinical outcome (p: 0.150) (Table 2).

Osserman classification showed most of the patients in Class IIa (43.7%), only 1 patient (6.3%) in Class I, 3 patients in Class IIb (18.7%), 3 patients in Class III (18.7%) and 2 patients in Class IV (12.6%) (Figure 3). All patients in lower Osserman group has achieved remission or improvement as compared to higher Osserman group (Grade III and IV), but no statistical correlation found between the Osserman group and the clinical outcomes (p: 0.225) (Table 3).

All 16 patients were received oral pyridostigmine (Mestinon) preoperatively with median doses of 285mg per day. Three patients were taking Mestinon, prednisolone and Azathioprine, one patient had taken Mestinon and steroid and one patient were taking Mestinon and Azathioprine. One patient had received intravenous immunoglobulin (IVIG) preoperatively. Post operatively, three patients were continuing with Azathioprine with reduced dose of Mestinon and one patient required plasmapharesis due to worsening of symptoms. One patient required added low dose of prednisolone post operatively.

There was one death following thymectomy in this study, due to worsening of symptoms induced by sedation during anaesthesia. This patient succumbed to death on day 11 after the operation due to severe septic shock secondary to fulminant chest infection. Two patients had minor anaesthesia-related complications with atelectasis and mild pleural effusion. Both were treated with chest physiotherapy and observation respectively. One patient was noted to have mild chest pain and treated with analgesia only.

**Discussion**

Thymectomy has been considered as an effective treatment compliment the medical therapies since Blalock et al. (3) had introduced this procedure with good outcome. It has been considered as a treatment of choice since 54 to 94% improvement rates and 13 to 46% remission rates seen in previous study (4, 5). Similarly, our study showed good outcome with total benefit rate was 87.5% and 12.5% showed clinical unchanged/worsening rates (Figure 1). Despite promising results seen, the selective of patients and specific indications for surgery remain unclear. Generalised disease, severity of symptoms, response to medication, and duration of disease and presence of thymoma were criteria reserved for this procedure (6). About 90% of our local populations are Malay with the remaining deriving from Chinese, Siamese and Indian roots. This consistent we our data whereby Malay population comprises the highest number and the remaining were Chinese. No representatives from Indian population as they are minority population with limited case were referred to neurosurgical clinic in HUSM. We found that males are more preponderance than female and inconsistent to the previously published studies that female was the predominant group. The atypical gender preponderance
may affect the clinical outcome in this study as previous study found that female patients responded better than male (4). In contrast, other study found that gender had not affected the clinical outcome (7).

We found no statistically significant in median follow-up between remission/improvement groups with unchanged/worst group. Nieto et al (7) in their study showed 46% achieved complete remission at five years follow-up. Maggi et al. (8) found that the remission is higher in patient with follow-up period of 5 to 10 years. Similar to this finding, Stern et al. (9) achieved greatest remission rates and symptoms improvement in patients with follow-up over 10 years. This has shown that follow-up period of five years and longer could have achieved more remission in our study following thymectomy.

Various histology findings were reported to have an impact in the clinical outcome after thymectomy. Approximately 10-15% of patients with MG are associated with thymoma. MG patients with thymoma had worse prognosis than MG patients with thymus hyperplasia (10). A study done by Hsu HS et al. (11) found that patients with thymoma had a greater possibility to develop relapse of symptoms after thymectomy than the patients without thymoma. In contrast, our study showed that all three patients with thymoma had demonstrated good outcome. In contrast, Tsinzerling et al. (12) found no significant differences in the outcome between several histology results.

Based on immunological role of thymus in MG, complete removal of thymus gland is crucial. The thymus gland arises from the third and fourth branchial arch. It migrates in a caudally manner and the lower lobes tend to leave scattered thymic tissue on the mediastinal fat (13). Thymus gland believed to be a source of T-cell population which will cause destruction of the anticholinesterase receptor, thereby produces weakness in MG (14). There is still unclear about the choice of surgery in order to ensure complete removal of thymus gland with scattered thymic tissue on mediastinal fat. However, extended thymectomy has shown in previous study to be an excellent operative procedure. It is suitable for both thymomatous and nonthymomatous patients (15). Extended thymectomy through transcervical or transternal approach and a new approach via video-assisted thoracoscopic thymectomy had shown promising results in either technique (16). Based on this outcome, inability to remove the entire residual thymus gland via either technique will eventually causing relapse. The transternal approach with anterior mediastinal dissection has been considered a good technique in ensuring complete removal of thymus tissue. This technique which has been used in our center demonstrated favorable outcome comparable to previous study. Furthermore, single surgeon who did the operation for all cases made the value more reliable.

Osserman classification has shown strong association with clinical outcome from previous study. Ozdemir et al. (17) found sevenfold increased risk of clinical worsening in patients with stage IIB and III. Nieto et al. (7) found that patients with stage I and III had a better outcome. Similar to this findings, Venuta et al. (18) found that patients with lower Osserman stage had shown favourable outcome. We found that patients in our study has better clinical outcome in stage I to II but statistically no significant exist in between Osserman stage and clinical outcomes.

Controversy exists regarding the need for thymectomy in ocular MG. However, it takes into consideration when 85% to 90% of individual with ocular MG eventually progress to generalised disease within 2 years (19). Masaoka et al. (14) found that thymectomy was effective in treating ocular MG. Delayed remission after thymectomy in patient with pure ocular MG observed by Nakamura et al. (20). Patient with short duration of illness prior to thymectomy has achieved faster remission rates in this type of patient (21). In our study, only one patient with ocular MG underwent this procedure. Thymectomy has shown to be an effective treatment for him as improvement in symptoms with no drug required postoperatively for a total duration of follow-up of 40 months.
Thymectomy has been considered as a safe procedure with low mortality and morbidity (22). In our study, only one patient succumbed to death due to myasthenia crisis induced by sedation. This patient was diagnosed at the age of 78 with Osserman stage III and thymoma. Other study has shown that old age at diagnosis and Osserman stage III and above was associated with a less favourable prognosis (23). Takanami et al. (24) found that involvement of bulbar muscle prior to the surgery was a significant risk factor for myasthenia crisis. A multicenter follow-up study done in Italy found that men, older than 40 years old, a short history of disease and with thymoma were associated with higher mortality rates (25).

Our study has several limitations. Firstly, this 10-year retrospective study might be biased due to missing data especially concerning the symptoms of patient pre and postoperatively. Secondly, this study has small sample size and the non-significant (P-values > 0.05) are expected in this small study. The findings reflect a single institution review and possibly left out important data pertaining to thymectomy for MG in Malaysia. Thus, multicenter involvement with a larger number of patients will be a future aim. Involvement of multiethnic Malaysian population is another issue to address in future research.

**Conclusion**

Thymectomy is perhaps an effective mode of treatment with lower surgical morbidity observed. This single centre study has shown that majority of patients benefited from thymectomy with tremendous clinical improvement and drug reduction postoperatively. Utilising multicentre studies is importance in future to improve power of study and will increase generalisability of the results. Thymectomy for ocular MG also had shown improvement postoperatively.

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The results of this study have been presented as a poster at Malaysia-Singapore Joint Ophthalmic Congress 2013.

**Conflict of Interest**

None

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None

**Authors’ Contributions**

Conception and design: JM, CCY
Analysis and Interpretation of the data: JM, CCY
Drafting of the article: JM, CCY
Critical revision of the article for important intellectual content: WHWH, ZMG
Final approval of the article: WHWH, ZMG
Provision of study materials or patients: ZMG
Administrative, technical, or logistic support:
Collection and assembly data: JM, CCY

**Correspondence**

Professor Dr. Wan Hazabbah Wan Hitam
References


**Outcomes of surgery**

- 1 Patient: Remission
- 2 Patients: Improvements
- 16 patients: No change
- 1 Patient: Worsening

Figure 1: Outcomes of surgery

**Histology of resected thymus gland**

- 3 Patients: Normal thymus tissue
- 1 Patient: Thymus hyperplasia
- 12 Patients: Thymoma

Figure 2: Histology of resected thymus gland
Table 1: Summary of clinical course of 16 patients in this study.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Age (year)</th>
<th>Race</th>
<th>Sex</th>
<th>Duration of symptoms (months)</th>
<th>Osserman Classification</th>
<th>Histopathologic study</th>
<th>Outcome</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>37</td>
<td>Malay</td>
<td>Female</td>
<td>3</td>
<td>III</td>
<td>Thymoma</td>
<td>Improvement</td>
</tr>
<tr>
<td>2</td>
<td>22</td>
<td>Chinese</td>
<td>Male</td>
<td>4</td>
<td>IIb</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
<td>3</td>
<td>75</td>
<td>Malay</td>
<td>Male</td>
<td>8</td>
<td>III</td>
<td>Hyperplasia</td>
<td>Worse</td>
</tr>
<tr>
<td>4</td>
<td>48</td>
<td>Malay</td>
<td>Female</td>
<td>60</td>
<td>IV</td>
<td>Thymus</td>
<td>No change</td>
</tr>
<tr>
<td>5</td>
<td>37</td>
<td>Malay</td>
<td>Male</td>
<td>60</td>
<td>IV</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
<td>6</td>
<td>32</td>
<td>Malay</td>
<td>Female</td>
<td>72</td>
<td>IIb</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
<td>7</td>
<td>47</td>
<td>Malay</td>
<td>Male</td>
<td>18</td>
<td>IIa</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
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<td>45</td>
<td>Chinese</td>
<td>Male</td>
<td>120</td>
<td>IIa</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
<td>9</td>
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<td>Malay</td>
<td>Female</td>
<td>9</td>
<td>IIa</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
<td>10</td>
<td>49</td>
<td>Malay</td>
<td>Male</td>
<td>3</td>
<td>III</td>
<td>Hyperplasia</td>
<td>Remission</td>
</tr>
<tr>
<td>11</td>
<td>38</td>
<td>Malay</td>
<td>Female</td>
<td>2</td>
<td>IIa</td>
<td>Thymus</td>
<td>Improvement</td>
</tr>
<tr>
<td>12</td>
<td>25</td>
<td>Malay</td>
<td>Male</td>
<td>10</td>
<td>IIa</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
<tr>
<td>13</td>
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<td>Male</td>
<td>10</td>
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<td>Thymoma</td>
<td>Remission</td>
</tr>
<tr>
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<td>Male</td>
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<td>I</td>
<td>Thymoma</td>
<td>Improvement</td>
</tr>
<tr>
<td>15</td>
<td>58</td>
<td>Malay</td>
<td>Male</td>
<td>6</td>
<td>IIa</td>
<td>Thymus</td>
<td>Improvement</td>
</tr>
<tr>
<td>16</td>
<td>26</td>
<td>Malay</td>
<td>Female</td>
<td>24</td>
<td>IIa</td>
<td>Hyperplasia</td>
<td>Improvement</td>
</tr>
</tbody>
</table>

Table 2: Clinical presentation of patient with Myasthenia Gravis who underwent Thymectomy in HUSM

<table>
<thead>
<tr>
<th>Variables (n = 16)</th>
<th>Percentage %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ptsosis (18.3%)</td>
<td>13</td>
</tr>
<tr>
<td>Limb weakness (87.5%)</td>
<td>14</td>
</tr>
<tr>
<td>Diplopia (43.8%)</td>
<td>7</td>
</tr>
<tr>
<td>Dysphagia (75%)</td>
<td>12</td>
</tr>
<tr>
<td>Variables</td>
<td>Outcome</td>
</tr>
<tr>
<td>---------------------------------------</td>
<td>----------------------------------</td>
</tr>
<tr>
<td>Histology of resected thymus gland ($n = 16$)</td>
<td>Remission/Improvements</td>
</tr>
<tr>
<td>Normal thymus tissue</td>
<td>0</td>
</tr>
<tr>
<td>Thymus hyperplasia</td>
<td>11</td>
</tr>
<tr>
<td>Thymoma</td>
<td>3</td>
</tr>
<tr>
<td>Osserman classification ($n = 16$)</td>
<td></td>
</tr>
<tr>
<td>Grade I</td>
<td>1</td>
</tr>
<tr>
<td>Grade IIa</td>
<td>7</td>
</tr>
<tr>
<td>Grade IIb</td>
<td>3</td>
</tr>
<tr>
<td>Grade III</td>
<td>2</td>
</tr>
<tr>
<td>Grade IV</td>
<td>1</td>
</tr>
<tr>
<td>Follow up time (Median)</td>
<td>34.5</td>
</tr>
</tbody>
</table>

*a Fishers exact test, *b Mann Whitney test. Significant $P$-value < 0.001