Extended transcervical thymectomy with partial upper sternotomy: results in non-thymomatous patients with myasthenia gravis

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Abstract

OBJECTIVES: Thymectomy is a recognized treatment for myasthenia gravis (MG), but the optimal surgical approach is yet to be determined. This study analysed the results in non-thymomatous MG patients treated at our institution using an extended transcervical access with partial upper sternotomy (TC-US), in order to describe cumulative incidence of remission and its predictors.

METHODS: In the period 1988–2012, 215 non-thymomatous MG patients underwent thymectomy using the TC-US approach. There were 61 males and 154 females (median age: 33 years). Primary end points were complete stable remission (CSR) and pharmacological remission (PR). Clinico-pathological predictors of CSR/PR were analysed including age, gender, preoperative MG symptom duration, preoperative immunosuppression therapy and disease severity.

RESULTS: The median follow-up period was 127 months. The median preoperative duration of MG symptoms was 9 months (interquartile range 4–13). The median operative time was 65 min (range: 45–135). There was no postoperative death. Morbidity rate was 7% (14 patients, no major complication). Ten patients died at the follow-up (3 of MG). MG symptoms improved in 85% (150/176) of the patients. CSR rate was 34%, PR rate was 4%. Cumulative incidence of CSR/PR was 27, 37 and 46% at 5, 10 and 15 years, respectively. Independent predictors of increased CSR/PR rate were age (P = 0.028) and MG symptom duration <6 months (P = 0.013).

CONCLUSIONS: Our data suggest that in patients with non-thymomatous MG, thymectomy by TC-US has a remission rate not inferior to those reported after trans-sternal or video-assisted thoracic surgery techniques. The short duration of MG symptoms before thymectomy is a predictor of remission. The technique strikes a reasonable balance between the extent of thymic resection, operative and anaesthesia time, patient acceptance, neurological outcome and costs.

Keywords: Myasthenia gravis • Thymus • Thymectomy • Outcomes

INTRODUCTION

Myasthenia gravis (MG) is a disorder of the neuromuscular transmission for which a clear pathophysiological basis and diagnostic modalities are well-defined. Conversely, a significant debate exists about the role of thymectomy in the management of the disease. Nonetheless, a number of non-randomized studies reported improvement in 60–95% of MG patients following thymectomy, and ~30% of patients experience a drug-free complete stable remission (CSR) [1].

Once the empirical role of thymectomy is established, the next issue is the optimal surgical access. Although the first thymectomy was performed transcervically in 1912, the trans-sternal access gained popularity in the 1980s following the results of Jaretzki et al. [2] who recommended a ‘maximal transcervical–trans-sternal thymectomy’ for non-thymomatous MG patients. Since then, the trans-sternal approach has been employed and described with different modifications [3]. In 1988, Cooper et al. [4] described an extended transcervical approach using a dedicated self-retaining retractor to lift the sternum during the operation. The debate between transcervical and trans-sternal accesses continued during the following years, further complicated by the introduction of video-assisted thoracic surgery (VATS) [5] and robotic-assisted thoracic surgery (RATS) [6] approaches. Overall, over the last 40 years more than 14 different surgical accesses have been proposed for thymectomy with different and often controversial results.
The present study reports our experience with the use of an extended transcervical thymectomy using a partial upper sternotomy in patients with non-thymomatous MG, which has been employed in our Unit in the last 30 years. Description of the technique, neurological outcomes and predictors of remission have been analysed.

MATERIALS AND METHODS

In the period 1988–2012, a total of 327 thymectomies in patients with MG were performed at our institution. Of these, 94 patients with thymoma and 9 with uncertain/missing diagnosis were excluded. Of the 224 patients with non-thymomatous MG, 7 patients receiving thymectomy through a full median sternotomy, and 2 through a VATS approach were also excluded from the analysis. The remaining 215 patients received a thymectomy through an extended transcervical access with a partial upper sternotomy and constitute the patient population of the present study. The medical records, operative notes and pathology reports were reviewed. The follow-up was conducted through a questionnaire, by telephone contacts, to the patients and their family doctors, which were conducted by the referring thoracic surgeon and neurologist. Informed consent was obtained in all patients.

Operative technique

Our technique of thymectomy in non-thymomatous MG patients has remained substantially unchanged during the study period and has been described elsewhere [7, 8]. It is classified as T-1c according to the Myasthenia Gravis Foundation of America (MGFA) thymectomy classification [9] with removal of all visible thymic tissue, encapsulated and extracapsular in the mediastinal fat. In brief, the patient is placed in a supine position with the neck hyperextended. A single-lumen endotracheal tube is employed. A 4 cm cervical incision is performed 1–2 fingerbreadths above the sternal notch; subplatysmal flaps are prepared superiorly up to the thyroid gland and inferiorly down to mid-sternum. The strap (infrahyoid) muscles sternohyoid and sternothyroid are separated along the midline. The mid-cervical fascia is incised and the two thymic upper poles are exposed and ligated from the thyrothymic ligament. The thymus with its capsule is freed from the posterior connective cervical tissue down to the sternal notch. Through the same cervical incision the upper portion of the sternum is then exposed and a partial upper sternotomy (6–8 cm) is performed. A dedicated V-shaped sternal spreader (Fig. 1) is inserted and the mediastinum is then accessed. Thymectomy is then completed through ligation/section of the thymic vein(s) at its origin from the left innominate vein. The mediastinal pleura is gently separated from the mediastinal fat tissue bilaterally. Using a peanut the mediastinal pleura is gently separated from the mediastinal fat tissue bilaterally. The dissection is conducted down to the pericardium and laterally to both phrenic nerves. The thymus and its capsule are then resected along with the mediastinal fat. A drain is placed retrosternally, which is removed on postoperative day 1. In case of inadvertent opening of the mediastinal pleura, a small-bore pleural catheter is inserted which is removed either at the end of the operation or the day after surgery. In uncomplicated cases, the patient is discharged on postoperative day 2.

Clinical assessment and neurological outcome

In the present study, the MGFA standards of measurements have been followed [10]. In particular, five pretreatment classes of clinical severity have been considered (Class I–V). After thymectomy, postintervention status was assessed using the MGFA categories: (i) complete stable remission (CSR); (ii) pharmacological remission (PR); minimal manifestations (MMs), further subdivided into MM-0, MM-1, MM-2 and MM-3 subclasses (MM classes recognize the patients who had weakness that was only detectable by careful examination). Furthermore, change in status included the following conditions: (i) improved; (ii) unchanged; (iii) worse; (iv) exacerbation and (v) died of MG. For the computation of the remission rates and cumulative incidence of remission, as suggested by other authors [11, 12], we included both CSR and PR in the definition of a complete remission. This results from the frequent attitude from neurologists to maintain a low-dose, single drug immunosuppressive therapy (<10 mg/day Prednisone or <150 mg/day Azathioprine) for many years despite absence of MG symptoms after thymectomy because of reports of relapses occurring in this setting.

Statistical analysis

Primary end points were the CSR and PR. The Nelson–Aalen method was used to compute the cumulative incidence of remission (CIR). To evaluate the association between variables of interest and remission, univariate and multivariate logistic regression were employed. Evaluated predictors included gender, age (both

Figure 1: Dedicated V-shaped sternal spreader.
as continuous and as categorical variable, in the latter case using the median age of the patient population as cut-off; pretreatment MGFA clinical classification (Class I as reference); duration of MG symptoms before thymectomy (both as continuous and as categorical variable); preoperative medical therapies (immunosuppression, anticholinesterase therapy). The statistical analysis was performed using STATA (StataCorp LP, Texas, US, version 12.1).

RESULTS

Demographics and clinical characteristics

Patient demographics and clinical characteristics are illustrated in Table 1. Most patients were female (n = 154, 71%). Median age was 33 years [interquartile range (IQR): 25–44 years]. Median duration of MG symptoms before thymectomy was 9 months (IQR: 4–13). According to the MGFA clinical classification (n = 208), about half of the patients were in clinical class II (n = 109, 52%), 44 (22%) in Class III, 34 in Class I (16%) and 17 (8%) and 4 (2%) were in Classes IV and V, respectively. Most patients were on anticholinesterase therapy at surgery and preoperative therapies were not independent predictors of remission. At multivariate analysis, similar predictors of remission were observed: age (HR: 0.97, 95% CI: 0.94–1.00) and MG symptom duration <6 months before thymectomy (HR: 2.35, 95% CI: 1.26–4.40). At multivariate analysis, similar predictors of remission were observed: age (HR: 0.97, 95% CI: 0.94–1.00) and MG symptom duration <6 months before thymectomy (HR: 2.40 95% CI: 1.20–4.81). Conversely, gender, MGFA clinical classification at surgery and preoperative therapies were not independent predictors of remission at either univariate or multivariate analysis.

Table 1: Patient demographics and characteristics

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>%</th>
<th>Median (IQR)</th>
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<tbody>
<tr>
<td>Gender (female)</td>
<td>154</td>
<td>72</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
<td></td>
<td>33 (25–44)</td>
</tr>
<tr>
<td>MG symptom duration before thymectomy (months)</td>
<td></td>
<td></td>
<td>9 (4–13)</td>
</tr>
<tr>
<td>MGFA clinical classification (n = 208)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>34</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>109</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>Class III</td>
<td>44</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Class IV</td>
<td>17</td>
<td>8</td>
<td></td>
</tr>
<tr>
<td>Class V</td>
<td>4</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Preoperative therapy (n = 203)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No therapy</td>
<td>26</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Immunosuppression</td>
<td>6</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Anticholinesterase</td>
<td>126</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Anticholinesterase + Immunosuppression</td>
<td>45</td>
<td>22</td>
<td></td>
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</tbody>
</table>

IQR: interquartile range; MG: myasthenia gravis.

Table 2 illustrates univariate and multivariate models for predictors of complete remission (CSR + PR). At univariate analysis, the following covariates were significant associated with remission: young age, as continuous (hazard ratio (HR): 0.97, 95% CI: 0.95–1.00) and short (<6 months) duration of MG symptoms before thymectomy (HR: 2.35, 95% CI: 1.26–4.40). Table 2 illustrates univariate and multivariate models for predictors of complete remission (CSR + PR). At univariate analysis, the following covariates were significant associated with remission: young age, as continuous (hazard ratio (HR): 0.97, 95% CI: 0.95–1.00) and short (<6 months) duration of MG symptoms before thymectomy (HR: 2.35, 95% CI: 1.26–4.40). At multivariate analysis, similar predictors of remission were observed: age (HR: 0.97, 95% CI: 0.94–1.00) and MG symptom duration <6 months before thymectomy (HR: 2.40 95% CI: 1.20–4.81). Conversely, gender, MGFA clinical classification at surgery and preoperative therapies were not independent predictors of remission at either univariate or multivariate analysis.

DISCUSSION

The results of this study on a population of non-thymomatous patients with MG submitted to thymectomy through an extended transcervical approach with partial upper sternotomy indicate that: (i) this technique achieves CSR rates and symptom improvement comparable with trans-sternal or VATS/RATS techniques; (ii) a young age and a short duration of MG symptoms before thymectomy are significantly associated with CSR; (iii) the technique can be safely performed with no need for one-lung ventilation or routine opening of pleural spaces and with minimal associated morbidity.

Despite its wide acceptance among thoracic surgeons, thymectomy remains controversial among neurologists as the optimal treatment in patients with MG. The MGFA, in 2000, considered thymectomy no more than ‘an option’ among treatments for non-thymomatous MG patients [10]. Despite this statement, however, confirmations of the efficacy of thymectomy continue to accumulate in the literature [13]. After recognition of the role of thymectomy, a further controversial issue remains the optimal surgical approach. Over the past 40 years a number of techniques have been proposed for thymectomy, which has generated a great confusion in the comparison of the results. A major contribution in clarifying this issue resulted from the MGFA Thymectomy Classification, recently modified by Sonett and Jaretzki [9]. The classification takes into consideration the presumed extent of the thymic resection and includes five major thymectomy groups (transcervical [T-1], videoscopic [T-2], transternal [T-3], combined transcervical–trans-sternal [T-4], infrasternal [T-5]), each further subdivided into subgroups. The transcervical approach (TCT) T-1 includes the basic TCT (T-1a), the extended TCT (T-1b), the extended TCT with partial sternal split (T-1c) and the extended TCT with videoscopic technology (T-1d).
The choice of the optimal surgical approach for thymectomy should consider different points: the neurological outcome, which is primarily dependent upon the extent of the mediastinal tissue resection, the potential morbidity of the technique and patient satisfaction.

It has been demonstrated without controversy that the success of thymectomy for MG primarily depends upon the amount of thymic tissue resected. It has been evident from the literature that regardless of the selected technique, the actual amount of thymic tissue resected depends upon the surgeon’s commitment in pursuing the resection in terms of time and meticulous search for ectopic thymic tissue as well as the surgeon’s experience with the technique employed. On the other hand, thymectomy for MG is a potentially morbid operation which is often performed in fragile,

Figure 2: Overall cumulative incidence of remission in our patient population.

Figure 3: Cumulative incidence of remission by the duration of MG symptoms before thymectomy (<6 vs >6 months). MG: myasthenia gravis.
Table 2: Univariate and multivariate analysis of predictors of remission (logistic regression—CSR + PR)

<table>
<thead>
<tr>
<th></th>
<th>Hazard ratio</th>
<th>Standard error</th>
<th>P-value</th>
<th>Lower</th>
<th>Upper</th>
<th>Hazard ratio</th>
<th>Standard error</th>
<th>P-value</th>
<th>Lower</th>
<th>Upper</th>
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</thead>
<tbody>
<tr>
<td>Gender (male vs female)</td>
<td>0.94</td>
<td>0.33</td>
<td>0.857</td>
<td>0.47</td>
<td>1.88</td>
<td>1.24</td>
<td>0.42</td>
<td>0.925</td>
<td>0.47</td>
<td>2.28</td>
</tr>
<tr>
<td>Age (continuous)</td>
<td>0.97</td>
<td>0.01</td>
<td>0.024</td>
<td>0.95</td>
<td>1.00</td>
<td>0.97</td>
<td>0.01</td>
<td>0.028</td>
<td>0.94</td>
<td>1.00</td>
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<tr>
<td>MGFA (class I as references)</td>
<td></td>
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<tr>
<td>Class II</td>
<td>0.84</td>
<td>0.37</td>
<td>0.691</td>
<td>0.35</td>
<td>2.00</td>
<td>0.98</td>
<td>0.49</td>
<td>0.962</td>
<td>0.37</td>
<td>2.59</td>
</tr>
<tr>
<td>Class III</td>
<td>0.82</td>
<td>0.41</td>
<td>0.685</td>
<td>0.31</td>
<td>2.17</td>
<td>0.94</td>
<td>0.52</td>
<td>0.914</td>
<td>0.32</td>
<td>2.76</td>
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<tr>
<td>Class IV</td>
<td>0.99</td>
<td>0.62</td>
<td>0.744</td>
<td>0.17</td>
<td>3.35</td>
<td>1.34</td>
<td>0.90</td>
<td>0.662</td>
<td>0.36</td>
<td>5.02</td>
</tr>
<tr>
<td>MG length ≤ 6 months</td>
<td>2.35</td>
<td>0.75</td>
<td>0.008</td>
<td>1.28</td>
<td>4.40</td>
<td>2.42</td>
<td>0.85</td>
<td>0.013</td>
<td>1.20</td>
<td>4.81</td>
</tr>
<tr>
<td>Preoperative therapy (no therapy as references)</td>
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<tr>
<td>Immunosuppression</td>
<td>2.40</td>
<td>0.75</td>
<td>0.008</td>
<td>1.28</td>
<td>4.40</td>
<td>2.42</td>
<td>0.85</td>
<td>0.013</td>
<td>1.20</td>
<td>4.81</td>
</tr>
<tr>
<td>Anticholinesterase</td>
<td>1.08</td>
<td>0.49</td>
<td>0.857</td>
<td>0.45</td>
<td>2.63</td>
<td>1.19</td>
<td>0.58</td>
<td>0.724</td>
<td>0.46</td>
<td>5.02</td>
</tr>
<tr>
<td>Anticholinesterase + immunosuppression</td>
<td>0.62</td>
<td>0.34</td>
<td>0.376</td>
<td>0.21</td>
<td>1.80</td>
<td>0.65</td>
<td>0.39</td>
<td>0.474</td>
<td>0.20</td>
<td>2.13</td>
</tr>
</tbody>
</table>

CSR: complete stable remission; PR: pharmacological remission; MG: myasthenia gravis.
the patients reported an improvement of their MG symptoms. We believe that our procedure offers significant advantages over other more invasive techniques. First, the surgical incision is limited to a 4-cm cervical incision, through which a partial upper sternotomy can easily be performed. Secondly, the procedure is conducted through a single-lumen endotracheal tube, thus eliminating the potentially dangerous period of one-lung ventilation in myasthenic patients. Thirdly, the operative time is \(~1\) h with a reduced anaesthesia time, the pleural spaces are not routinely opened, no pleural drainages are positioned and the patient is extubated in the operative theatre. Finally, the costs of the procedure are far less in terms of surgical/anaesthetic equipment, operative theatre occupation time and postoperative stay than any other surgical access. We therefore believe that our technique can fulfill all the requirements to be considered as minimally invasive for this specific and delicate group of patients.

Table 3 reports crude remission rates and CSR rates by Kaplan–Meier analysis of recent series using different thymectomy approaches. From the table it appears that crude remission rates range from 37 to 46\% after trans-sternal approaches vs 21\% to 38\% after transcervical approaches. The CSR rates based on the Kaplan–Meier analysis, which are far more reliable outcome measurements, also overlap, although this is less frequently reported. Series reporting VATS/RATS thymectomy are more difficult to compare because of the different techniques employed, the relatively few series with an adequate number of enrolled patients and the shorter follow-up.

In the largest VATS/RATS thymectomy series, crude CSR vary from 14 to 40\% and CSR rates based on the Kaplan–Meier analysis are \(~30–40\%) at 5 years, which is thus comparable to those after transcervical approaches. It may be suggested therefore that when a thymectomy is performed by experienced operators, no single approach seems to be significantly superior to the others, and any superiority of more extended, invasive approaches may likely be outweighed by the increased morbidity and less patient satisfaction. In the present study, our results compare favourably with most of the studies using other techniques.

Our study also indicates that some predictors of complete remission might be identified and should be taken into account by the neurologists in the referral of the patients to the surgeon. In particular, a short (<6 months) duration of MG symptoms before thymectomy was found to be significant predictors of remission. A study from our institution on a previous time period (1973–1987) showed similar predictors [7]. Many studies have been published in the recent literature evaluating clinico-pathological predictors of remission in patients with MG. Female sex [13, 22], young age [13, 22, 24], short preoperative MG symptom duration [24], mild MG clinical severity [6, 17], no preoperative steroid therapy [3, 24], thymic hyperplasia [13], the absence of thymoma have all variously been correlated with improved remission rates.

The present study has some strengths and some limitations. Among the strengths there is the long experience of our group in the management of MG patients, resulting in a homogeneous diagnostic and follow-up protocol and a consistent surgical approach which has remained substantially unchanged over the last 40 years. Other strengths include the reasonably small percentage of patients lost to the follow-up, the adoption of the MGFA standards of measurements for post-resectional status, thymectomy classification and the life-table analysis for the calculation of the CSR. Among the limitations, there are the retrospective nature of the study and the lack of a control group from the same institution submitted to an alternative surgical approach (trans-sternal or VATS).

In conclusion, our results on a population of non-thymomatous patients with MG receiving extended transcervical thymectomy with partial upper sternotomy demonstrate that this approach strikes a balance between the extent of thymic resection, morbidity, results and costs and supports its use.

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REFERENCES