Thymectomy in Myasthenia Gravis: A Narrative Review

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INTRODUCTION

Myasthenia gravis (MG), the most common neuromuscular junction disorder, is an autoimmune disorder caused by autoantibodies directed against acetylcholine receptors (AChR) on postsynaptic membrane, causing defective transmission at the neuromuscular level and leading to fatigable muscle weakness. Very recent global epidemiological data has estimated the prevalence of MG to be 12.4/100,000.1,2 In early-onset MG, women are more commonly affected before age of 40 years, with a female: male ratio of 3:1.3 About 7 of 10 patients with MG have thymic follicular hyperplasia and up to 15% of the patients are diagnosed with thymoma. Up to 40% of patients who have thymoma experience symptoms associated with MG.4-8 Treatment modalities for MG include acetylcholinesterase inhibitors, immunotherapy, immunomodulation, monoclonal antibodies and thymectomy.

The use of thymectomy as a treatment modality has steadily increased since its benefits were first described in 1940. The only randomized trial comparing thymectomy to medical management of MG has established that thymectomy leads to better outcomes in non-thymomatous generalized MG. However, thymectomy remains controversial in some disease subtypes and there are concerns regarding the best surgical approach for achieving complete removal of the thymic tissue, and thus achieve stable remission rates. This review highlights the role of thymectomy in non-thymomatous and thymomatous MG, the effectiveness of various thymectomy methods, postoperative myasthenic crisis, and remission after thymectomy.

Keywords: Acetylcholine receptors, myasthenia gravis, thymectomy, thymoma

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critical review of the literature is warranted based on the recent studies and updates on the treatment guidelines. Accordingly, this review was conducted with the objective of detailing the role of thymectomy in non-thymomatous and thymomatous MG, the effectiveness of various thymectomy methods, postoperative myasthenic crisis, and remission after thymectomy.

For this review, the authors searched the Cochrane Central Register of Controlled Trials, EMBASE, LILACS, and PubMed from 1900 up to December 2021, using the following keywords: “thymectomy”, “myasthenia gravis”, “non-thymomatous and thymomatous myasthenia gravis”, “myasthenic crisis”, and “remission”. There was no restriction regarding language or publication status. The authors assessed the abstracts of the available literature and reviewed the full texts of potentially relevant articles. In addition, the reference list of all articles was checked to identify relevant studies. All articles discussing the comparison of thymectomy to medical management for MG, methods of performing thymectomy, and peri-procedural care were included for the review.

**ROLE OF THYMUS IN THE PATHOPHYSIOLOGY OF MYASTHENIA GRAVIS**

The role of thymus in the pathophysiology of MG is well established. However, recent studies have further indicated that mice injected with dissociated thymic cells or thymic tissue from MG patient develop symptoms of MG.[10-16] In addition, glucocorticoid therapy results in reduction of germinal centers.[17] Frequently observed changes in the thymus gland of patients with MG, association between the degree of thymic follicular hyperplasia and titers of AChR antibodies, and evidence indicating improvement in patients with MG after thymectomy establish a causal link between thymic pathology and MG.[18]

**THYMECTOMY IN NON-THYMOMATOUS MYASTHENIA GRAVIS**

Based on review of available observational studies until 1998, the Quality Standards Subcommittee of the American Academy of Neurology recommended thymectomy as an option to increase the probability of remission or improvement in patients with nonthymomatous autoimmune MG.[19] It was also noted that patients with severe MG symptoms, females, and those who undergo thymectomy early after diagnosis had better post-surgical outcomes.

Thymectomy in patients with non-thymomatous MG has been shown to increase the likelihood of overall improvement, medication-free remission, and being asymptomatic compared with those treated medically. However, most such studies were observational, wherein the characteristics of patients in the thymectomy and non-surgical groups differed.[20] Nonetheless, in a single center retrospective study, the rate of complete stable remission (CSR) after thymectomy was found to be 27.7% at 10 years, 37.6% at 25 years and 47.3% at 40 years.[20]

Similar findings were observed in a systemic review where the odds of achieving remission was 2.4 times in patients with MG who underwent thymectomy in comparison with patients treated medically.[21] Similarly, in a meta-analysis, patients who underwent thymectomy were 2.34 times more likely to achieve remission than the non-surgical group.[22] Measurement of solid volume of thymus in 3D images, which contains almost all germinal centers, has been reported to predict the efficacy of extended thymectomy and post-thymectomy reduction in steroid dose in non-thymomatous MG patients.[23] A recent meta-analysis has identified patients’ preoperative conditions such as history of myasthenic crisis, bulbar symptoms, Osserman stages, dosage of pyridostigmine bromide prior to the surgery, AChR-Ab level >100 nm/L, abnormal lung function, major preoperative complications, and disease duration before thymectomy as independent risk factors of postoperative myasthenia crisis. In addition, surgery-related factors such as intraoperative blood loss >1000 mL and thoracotomy, and postoperative conditions such as lung infection, thymoma, and WHO classification were identified as independent risk factors of myasthenic crisis after thymectomy.[24] Patients with mild to moderate non-thymomatous MG who undergo thymectomy have been shown to require lesser doses of prednisone and bromopyrazine over a long-term.[25]

**Randomized trial of thymectomy in myasthenia gravis (MGTX trial)**

This was a multicentre, randomized trial that compared extended trans-sternal thymectomy plus prednisone therapy with prednisone therapy alone in non-thymomatous generalized MG.[9] Patients who underwent thymectomy showed improvement in their symptoms and their requirement of doses of prednisone was reduced, and thus had fewer side effects than patients in non-surgical group. Female patients who underwent thymectomy had better outcomes regarding symptoms and dose of prednisone. Patients who were already taking glucocorticoids before enrolment showed better results in the thymectomy group. Further, the study showed a significant reduction in the episodes of myasthenia exacerbation and associated hospitalization in the thymectomy group. In comparison to patients in the thymectomy group, more patients in
the prednisone group had treatment-related problems. Thymectomy was associated with a better quality of life, lesser patients requiring azathioprine, and more patients achieving minimal-manifestation status (MMS). This study had limitation that it compared only one method of thymectomy with medical management.

Almost half of the patients who participated in the MGTX trial were further followed up for 2 years. At the completion of 5 years, the difference in time weighted average QMG score between the two groups was even more evident than noted at 3 years. More patients achieved MMS in the thymectomy group and required smaller doses of prednisone (about 5 mg/day) in comparison to the prednisone-only group. Most of the results from the MGTX trial also showed consistency in favoring thymectomy over prednisone alone in the treatment of non-thymomatous MG during the extended follow-up for 2 years.[26] Recently, a post hoc analysis of the data from the MGTX trial provides a class II evidence that patients who received thymectomy plus prednisone are more likely to achieve sustained MMS and a complete withdrawal of prednisone compared to those managed with prednisone alone.[27]

In 2016, International Consensus Guidelines for Management of Myasthenia Gravis recommended thymectomy as an option in AChR antibody-positive non-thymomatous generalized MG patients (including those who develop intolerable side effects of immunotherapy or do not respond to it) to potentially avoid or minimize the dose or duration of immunotherapy. Same recommendations were made for children with generalized AChR antibody-positive MG. Thymectomy should be performed in most patients with thymoma except those who are elderly, have many comorbid conditions, and have small thymomas. Further, the guideline emphasized that less invasive approaches also have comparable results to open surgical approaches.[28] Similarly, the Association of British Neurologists’ management guidelines for MG recommends thymectomy as a reasonable treatment option in non-thymomatous MG patients who are <45 years of age and who have positive serum anti-Ach-R antibody. Patients should achieve optimum symptomatic control before thymectomy and an early surgery following the diagnosis should be considered for better outcome.[29]

In 2020, the updated International Consensus Guidance for Management of Myasthenia Gravis stated that thymectomy can be an elective and safe procedure in stable patients when postoperative pain and mechanical factors limit respiratory function. Considering the surgery at the early stage of the disease improves patient outcome and minimizes the requirements for immunotherapy and need for hospitalizations for disease exacerbations. In addition, thymectomy should be strongly considered if the patients with AChr-Ab+ generalized MG experience intolerable side effects to initial immunotherapy or fail to respond.[30]

Thymectomy in non-thymomatous ocular myasthenia gravis

Ocular MG (OMG) involves extraocular muscles and manifests as diplopia and ptosis. About half of all OMG patients progress to generalized MG over a period of 2 years.[31] The goal of treatment in OMG is to make vision better and halt its progression to generalized MG. Medical management of OMG consist of acetylcholinesterase inhibitor drugs, steroids, and other immunosuppressive agents. The role of thymectomy in non-thymomatous OMG patients remains controversial. Some studies have reported that thymectomy in patients with OMG can result in both improving symptoms and preventing its progression to generalized MG.[32-35] A meta-analysis of 26 studies with 640 subjects demonstrated that thymectomy in patients with non-thymomatous OMG resulted in 50% patients achieving CSR. In subgroup analysis, children and subjects from Western countries achieved better rates of CSR as compared to adults and the Asian population.[36]

Based on the EFNS/ENS Guidelines, thymectomy is not recommended for OMG as a first-line treatment; however, it should be considered if the patient is unresponsive to drug treatment and when tests indicate a high risk of progression to generalized disease in AChR-Ab+ generalized OMG.[37]

Similar recommendations were made in the International Consensus Guidance for Management of Myasthenia Gravis.[30]

Thymectomy in Anti-MuSK antibody-positive myasthenia gravis

Patients with anti-MuSK antibody-positive MG have prominent respiratory and bulbar symptoms. Most of these patients have normal thymus gland and few have thymic hyperplasia in comparison to AChR-Ab+ MG.[38]

In a post hoc analysis of anti-MuSK antibody-positive MG patients treated with and without thymectomy, the surgical intervention was not found to significantly improve the clinical outcome. In addition, there was no difference in the requirement of immunosuppressive agents between the groups, rather a higher dose of prednisone was required in the thymectomy group.[39] Therefore, thymectomy may have a limited role in the treatment of anti-MuSK antibody-positive MG, and additional controlled studies would provide more clarity.
Thymectomy in juvenile myasthenia gravis

Similar to thymectomy for adult MG, there is a paucity of prospective studies regarding thymectomy for juvenile MG. Observational studies have shown that thymectomy is effective in juvenile patients with MG. In a systemic review by Madenci et al., which included 16 studies with MG patients aged <18 years and 85% being AChR-Ab+, about one-third had CSR and 77% showed some improvement in their symptoms after thymectomy. Further, the rate of post-operative complications was between 0% and 30%. Only 4 of the 16 studies compared surgical approaches, and the results of those studies were mixed, as three studies found the thoracoscopic approach being non-inferior to transsternal approach regarding post-surgical reduction of disease severity, whereas one study reported that the rate of repeat thymectomy was higher in the group of patients who underwent thoracoscopic thymectomy. This review was unable to execute a meta-analysis due to the heterogeneity observed between patient's age, severity of MG, serology, and timing of surgery among the study population. In a retrospective study by Kim et al., 50 children with MG underwent thymectomy through the left thoracoscopic approach. Half of these patients had generalized MG and the remaining had OMG. About 50% of the patients improved and a significant trend toward reduction of steroid use was noted. In another retrospective study conducted in Germany, robotic-assisted thymectomy was found to result in clinical remission in 4 of 10 patients with juvenile generalized MG as well as the reduction in required dosages of immunosuppressants. The mean duration of postoperative hospital stay was 2.9 days. Overall, thymectomy has been found to be effective in the management of MG in reducing the severity of the disease and in the required dosage of immunosuppressants.

METHODS OF THYMECTOMY

Thymectomy for MG can be performed via the following surgical approaches:
• Transsternal approach
• Transcervical approach
• Combined transsternal and transcervical approach
• Minimally invasive approach: Video- or robot assisted

Open surgical approaches have been used for a long time and transcervical approach has been compared with medical management in randomized controlled trials. But interest in minimally invasive approaches has been growing recently. Minimally invasive approach for thymectomy has advantages of lesser or no pain, faster postoperative recovery, avoiding large scars, early mobilization, and early discharge from hospital with results comparable to open approaches such as transsternal and transcervical.

Video-assisted thoracoscopic thymectomy versus transsternal thymectomy

Bagheri et al., compared transsternal thymectomy with video-assisted thoracoscopic thymectomy (VATS) and found that VATS approach was associated with shorter intensive care unit stay, less blood loss, and higher rates of CSR. Despite the advantages and comparable outcome to sternotomy, the limited visibility in VATS results in limited resection of thymic tissue, particularly ectopic tissue, and the possibility of conversion to open approach in case of excessive bleeding.

Robotic-assisted thoracoscopic surgery

One of the minimally invasive approaches that has gained popularity in recent years is the robotic-assisted thoracoscopic (RATS) approach. The robotic approach offers additional advantages of magnified three-dimensional visualization of operative filed, increased liberty of instrument motion, and precise dissection in small anterior mediastinal space. It was first described in 2003 by Ashton et al. in a 28-year-old female with generalized MG associated with thymic hyperplasia. Ten years later, Marulli et al., reported their experience of left-sided robotic thymectomy in 100 patients. It was noted that 6% of the patients suffered postoperative complications, 28.5% had CSR, and 87.5% had overall improvement on follow-up. Thymic hyperplasia was found in 76% of the surgical specimens. Renaud et al. reported that robot-assisted thymectomy resulted in shorter hospital stay with similar results regarding myasthenia remission in comparison to standard sternotomy. In a study conducted by Rückert et al., it was reported that robotic thoracoscopic surgery resulted in improved remission rates in comparison to non-robotic thoracoscopic surgeries at follow-up of 3.5 years. In a prospective study, over 6 years, robotic-assisted thymectomy performed on 75 patients was found to result in early extubation, short intensive care unit stay, and an early return to pre-thymectomy activities; a significant improvement was seen in 87% of the patients.

Video-assisted thoracoscopic thymectomy versus robotic-assisted thoracoscopic surgery

Both minimally invasive approaches have advantages over the open approach and are being increasingly used for thymectomy in patients with MG. A meta-analysis of four studies that compared VATS and RATS found that although the operating time was lesser in the VATS group, there was no statistically significant difference for conversion to open thymectomy, blood loss, chest tube
drainage, or postoperative pneumonia.\textsuperscript{[52]} There were no in-hospital deaths in either group.

RATS has specific advantages such as better dexterity, precision, and stability as well as access to narrow regions and protection from injury to nerves. However, it is costly, requires a longer docking time, and there is possibility of conversion to sternotomy in case of emergency that would require undocking of robotic system and sterilization of the operator. RATS has been reported to be a safe and feasible approach for thymectomy in MG; however, data on long-term outcome are not yet available.

**Subxiphoid approach**

The subxiphoid approach was reported by Kido \textit{et al.} in 1999 and gained attraction in recent years. It comes with the advantage of recognizing both phrenic nerves as well as the location of the superior pole of thymus, avoiding injury to intercostal nerves, and satisfactory aesthetic results in case of a single port approach.\textsuperscript{[53,54]} Suda \textit{et al.} reported that the single port subxiphoid approach, offering better view and manipulation of instruments, is associated with equal operating time and lesser pain and blood loss in comparison to VATS.\textsuperscript{[55,56]}

The subxiphoid approach provides the advantage of minimizing the occurrence of intercostal neuropathy, enabling good visualization of bilateral phrenic nerves, and cervical region and rapid conversion to median sternotomy. However, instruments might not be long enough to reach the upper pole of thymus, resulting in limited resection of thymus gland.\textsuperscript{[57]}

**Choice of side for minimally invasive approaches**

Despite the increasing number of minimally invasive thymectomies performed, it is still debated on the preferred side (right, left, or bilateral). Surgical access can be right-handed or left-handed. The right-sided approach has the advantage of easier orientation of superior vena cava and pericardial and perithymic fat tissues. In addition, the aortopulmonary window can be removed completely, including any thymus gland tissues within it.\textsuperscript{[58]} Xie \textit{et al.}, compared thoracoscopic thymectomies performed either through the right or left side and found no difference in terms of surgical time, intraoperative blood loss, duration of postsurgical hospital stay, and postoperative complications.\textsuperscript{[59]} Tomulescu \textit{et al.} reported that VATS thymectomy using right- or left-sided approach is beneficial with no superiority of one side over the other.\textsuperscript{[60]} In a study on cadavers by Rückert \textit{et al.}, it was concluded that the left-sided approach is favorable in achieving a radical thoracoscopic thymectomy.\textsuperscript{[61]} Liu \textit{et al.} compared bilateral VATS with right-sided VATS in patients with non-thymomatous MG and did not find any significant difference in operative and long-term outcomes.\textsuperscript{[62]}

However, a recent multi-center review of 123 MG patients who underwent a minimally invasive thymectomy found left-sided thymectomy to be favorable over a right-sided approach considering the shorter operating time and better patient outcome.\textsuperscript{[63]}

Overall, minimally invasive approaches are effective, safe, and feasible and should be considered for thymectomy in MG patients at centers with expertise in these techniques. A recent meta-analysis on the effectiveness of the various surgical approaches to thymectomy in patients with MG observed a significant difference in the rate of CSR among various surgical techniques at long-term follow-up. They found equivalent CSR rates in extended minimally invasive approaches and extended transsternal approaches.\textsuperscript{[64]}

**Perioperative management**

Patients with MG undergoing thymectomy should be managed by a multidisciplinary team. A pulmonary function test needs to be performed preoperatively. Based on the patient’s preferences and comorbid conditions, either plasmapheresis or intravenous immune globulin should be considered to improve muscle weakness. Both treatments pose similar efficacy.\textsuperscript{[65]} Use of acetylcholinesterase inhibitors during the perioperative period may cause problems with the respiratory system, especially if used along with neuromuscular blocking agents. Corticosteroids may help with muscle weakness but might cause problems in wound healing. Drugs that cause worsening of weakness should be avoided.

**POSTOPERATIVE MYASTHENIC CRISIS AND REMISSION**

**Risk factors for postoperative myasthenic crisis**

Exacerbation of symptoms after thymectomy is a potential risk and may require mechanical ventilation. Leuzzi \textit{et al.} reported that a higher score on Osserman classification, body mass index of $>28$, history of myasthenic crisis, MG of $>2$ years duration, and lung resection were associated with increased risk of postoperative myasthenic crisis.\textsuperscript{[66]}

Presence of bulbar symptoms before surgery, high score on Quantitative Myasthenia Gravis Score, low forced vital capacity at baseline, decremental responses of orbicularis oris, and nasalis on low-frequency repetitive nerve stimulation were reported to be associated with a higher risk of myasthenic crisis after VATS surgery.\textsuperscript{[67]} Leventhal \textit{et al.} proposed a four-item scoring system to determine predictors for the postoperative need of mechanical ventilation in
patients with MG undergoing thymectomy (maximum score 34). Based on this, patients who score ≥10 require mechanical ventilation. A retrospective study by Chigurupati et al. reported that duration of MG and dose of pyridostigmine were not associated with the risk of prolonged mechanical ventilation after thymectomy. However, patients with a higher score on Osserman’s classification, history of myasthenic crisis prior to surgery, seropositivity for AChR antibodies, preoperative vital capacity <2.9 L, and presence of thymoma were associated with an increased risk of prolonged mechanical ventilation after thymectomy.\(^{[69]}\)

**Predictors of remission after thymectomy**

In a systemic review, lower scores on the Myasthenia Gravis Foundation of America (MGFA) severity scale (I-II) or Osserman classification (1/2A) were the only variables that were consistently associated with remission after thymectomy.\(^{[70]}\) A retrospective study conducted by Kim et al. also found that mild disease before thymectomy and non-thymomatous myasthenia was associated with achieving complete stable or pharmacologic remission.\(^{[71]}\) Zheng et al. reported that lower scores (I-II) on MGFA were consistently associated with remission of MG post-thymectomy.\(^{[72]}\) In a retrospective study by Jing et al., postpubertal and adult patients with non-thymomatous MG who received steroid therapy before thymectomy and for whom thymectomy was performed early had better chances of achieving remission. Delay from diagnosis to surgery was associated with lesser chances of remission.\(^{[73]}\)

**THYMECTOMY IN THYMOMATOUS MYASTHENIA GRAVIS**

Up to 15% of patients with MG are diagnosed with thymoma and up to 40% of patients who have thymoma experience symptoms associated with MG.\(^{[6-8]}\) In patients with thymomatous MG, myasthenic symptoms are more severe and the rate of post-thymectomy remission is much lower in comparison to non-thymomatous MG patients.\(^{[74-78]}\) With few exceptions, all patients with thymoma should undergo thymectomy.\(^{[28]}\) Patients with thymoma have about 1% to 3% risk of developing post-thymectomy MG with the major determinant being positivity for AChR antibodies.\(^{[8]}\) Neurologic symptoms need to be stabilized and intravenous immune globulin or plasmapheresis may be considered in cases of thymomatous MG with worsening symptoms.\(^{[79,80]}\) A retrospective study conducted by Li et al. reported a worse prognosis in patients with postoperative myasthenic crisis and found that defective resection of thymoma and the presence of bulbar symptoms before surgery are important risk factors.\(^{[81]}\) In addition, a study found that higher score on Osserman’s classification (IIA-IV) and WHO type B2-B3 thymomas were independently associated with a higher risk of postoperative myasthenic crisis.\(^{[82]}\)

**CONCLUSION**

Thymectomy results in clinical improvement in AChR antibody-positive MG patients. Minimally invasive thymectomy appears to be a valid treatment option for patients with both non-thymomatous and thymomatous MG. However, randomized controlled trials are required to establish the efficacy and long-term outcome of thymectomy in juvenile and geriatric patients and ocular and anti-MuSK antibody-positive subtypes of MG.

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