# Thymectomy in Non-Thymomatous Myasthenia Gravis: Does An RCT Solve The 75-Year-Old Controversy?

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## Abstract

The role of thymectomy in thymomatous myasthenia gravis (MG) is unambiguous. However, its role in non-thymomatous MG (NTMG) remains debatable. The evidence till date is not robust. In this short review, we try to see the pros and cons of thymectomy in NTMG and critically appraise the evidence available till date.

**Keywords:** Myasthenia gravis, non-thymomatous, thymectomy

The role of thymectomy in myasthenia gravis (MG) was recognized as early as 1939 when Alfred Blacock published a case report[1] describing successful outcome of a patient with thymoma and MG after undergoing thymectomy which was extended in non-thymomatous cases.[2] In 1966, a large case series comprising 1,355 patients with MG [including 188 non-thymomatous MG (NTMG)] was published. This retrospective study had a huge impact on neurology practice as it showed marked improvement in 51% and total remission in 38% in a subset of females younger than 40 years of age.[3]

At the same time, the role of thymus in pathogenesis of acetylcholine receptor antibody (AchRAb)-positive MG was described, suggesting that thymus has a key role in inducing AchRAb production.[4] Three subgroups of antibody-positive patients were identified and then further classified on the basis of age, sex, HLA association, and presence of myoid cells. The three groups identified were as follows: early onset with thymic hyperplasia, late onset with thymic atrophy, and finally, those with thymoma.[4]

The role of thymectomy in thymomatous MG is unambiguous as it is essential to remove any tumor from the body. However, its role in NTMG remains debatable. The evidence till date is based on 12 non-randomized observational retrospective series, one prospective cohort study, which relies on remission rates using Kaplan–Meier curves, and a single randomized controlled trial (RCT).

There is a lot of variability in these trials in terms of age of recruitment, duration and severity of disease, inclusion of patients with thymoma, surgical techniques used, use of concomitant immune-suppression (IS), and duration of post-surgical follow-up.

A review by Grosenth *et al*.[5] which included all non-randomized studies dating back to 1953 concluded that no class I studies have been performed and class II studies show higher remission rates in the thymectomy group.

A Cochrane review (2013) concluded that there are no published RCTs on this topic.[6] The consensus statement stated that "The value of thymectomy in the treatment of pre-pubertal patients with MG is unclear, but thymectomy should be considered in young adults with generalized AChR antibody–positive MG: If the response to pyridostigmine and IS therapy is unsatisfactory; or to avoid potential complications of IS therapy."[7]

The MGTX study group thus aimed to provide a class I evidence to solve this age-old controversy.[8] Recruitment was difficult as many experts were not very convinced in favor of thymectomy. (Supplementary appendix reported survey of 133 MGTX study investigators: 29 could not offer prediction, 27 felt that the outcome will not favor thymectomy, while 77 predicted that outcome would favor thymectomy.)

The MGTX randomization period encompassed of 6 years (2006–2012) at 36 centers and complete results were available after 3 years following the 36-month assessment protocol. The initial inclusion criteria comprised patients falling in the age group of 18–60 years with less than 3 years' duration of MG with elevated AchR antibody level and having Myasthenia Gravis Foundation of America (MGFA) clinical classification grade between II and IV, excluding patients with severe disease (MGFA grade V) and pure ocular manifestations (grade I).

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Primary outcomes were measured with time-weighted average Quantitative Myasthenia Gravis score (QMGS) (0–39) and time-weighted average required dose of prednisone over 3 years. As expected, the recruitment was challenging so eligibility criteria were expanded 2 years after the original enrollment. The age limit was extended from 60 to 65 years and the disease duration was increased from 3 to 5 years.

However, only 36 of 67 participating centers successfully recruited patients. Only 231 patients were found eligible of the total 6,958 patients screened, out of which 105 denied participation due to concern about either undergoing (45) or being denied (22) thymectomy. The remaining 126 participants (1.81% of screened population) were randomized to prednisone alone (N = 60) or thymectomy plus prednisone (N = 66) arms and both arms were well-matched at baseline.

At the time of randomization, both arms received prednisone with increasing dose starting from 10 up to 100 mg or 1.5 mg/kg, whichever was lesser in prednisone-naive patients and up to 120 mg/day in patients already on prednisone. Controversially, the former group who was doing well off steroids seems to have been forced upon to take prednisone, even when they did not seem to require it. Addition of steroids in well-controlled patients with MG also seemed unwarranted on two accounts: 1) to add steroids just to match the patients in protocol and 2) addition of steroids could actually prove detrimental in a disease like myasthenia, as it is known that steroids may worsen MG. Once the study target of "minimal manifestation" (MM) status was achieved, prednisone was tapered to the lowest dose needed to maintain MM status. The duration to achieve MM was not mentioned in this study.

Azathioprine (AZT) was added when there were unacceptable steroid-induced side effects or patients could not achieve MM status after 12 months of prednisone therapy, which is contrary to the established evidence of starting AZT along with prednisolone and sparing long-term use of prednisolone.[9]

Patients receiving other immunotherapies like mycophenolate mofetil, cyclosporine, tacrolimus, and methotrexate, which are not uncommon in use, were excluded. The trial was single-blinded and thymectomy was done within 30 days of randomization by extended median sternotomy approach.

It should be kept in mind that undergoing a major open surgery like thymectomy through open median sternotomy is in itself a big decision to make as the mortality rate after median sternotomy thymectomy is as high as 6.5%.[10]

Pre-existing anxiety (up to 45.3% of patients with MG have anxiety disorders) predisposes these patients to postoperative myasthenic crisis in up to 12.5% of patients,[11] which also adds to morbidity/mortality. But this study did not asses the preoperative mood changes.

In view of the currently available newer techniques such as video-assisted thoracoscopic surgery (VATS) and robotic surgery, which are lesser invasive and reduce perioperative morbidity and mortality, median sternotomy may not be an appropriate procedure to apply in current practice. Also, this trial does not mention the operative details about the extent and frequency of extra-thymic tissues.

The MGTX trial showed a statistically significant ($P < 0.01$) benefit at 3 years favoring thymectomy for both primary outcomes in the form of absolute reduction of 2.85 in the average QMG score (6.5 vs 8.99 in the prednisone-only group) and a lower average alternate-day prednisone requirement (44 vs. 60 mg in the prednisone only-group). The Task Force recommends to use QMG score in conjunction with clinical classification and postintervention status (PIS). It also recommends the use of PIS for documenting change in clinical status after any therapy.[5] The QMG score is a 39-point score based on endurance of specific muscle groups and an average difference of 2.85 may not be reflective of a significant clinical improvement. The secondary outcome measures provide additional supportive evidence. There were fewer hospitalizations for MG exacerbation/crisis (9 vs 37), as well as a reduced cumulative number of hospital days in the thymectomy group.

To summarize, this trial will continue to stand as a landmark study supporting thymectomy in NTMG. However, certain aspects like only limited patients getting qualified for randomization (1.8%), study population being limited to mild to moderate disease with relatively recent onset, and concurrent treatment with high-dose steroids may not be in line with daily practice. Also, whether lesser invasive techniques (e.g. VATS, etc.) can still offer the same benefit requires additional RCT. This trial did not include ocular MG and sero-negative MG which ultimately qualifies only about 50%–60% of MG cases as those who have ocular onset, those with MusK or LRP4 antibodies, as well as children and elderly population are excluded. Another weak point to add may be that as per the natural history of the disease, 10%–20% undergo spontaneous remission,[12] and putting these patients under surgical blade may be unnecessary. This point is also evident in the trial as the relative benefit of thymectomy becomes less prominent over time, with remission increasing from 37% to 47% at 3 years in the prednisone-only group.[13] Another limitation is short follow-up of 3 years, when it is known that relapse is common after 5 years of thymectomy[14] and the maximum benefit of thymectomy may not show until 5 years.[15] A recently published 5-year follow-up data showed a 60-month follow-up of only 45% study population enrolled in the original study (50 of 111 patients). It showed significantly lower time-weighted mean QMG scores and lower mean alternate day prednisone doses in thymectomy plus prednisone group.[16] However, in current practice none of us would continue to keep our patients on prednisone for 5 years and addition of steroid-sparing agents is inevitable. Keeping in mind that AZT is excellent drug to achieve remission,[17] now it is also time to weight efficacy of thymectomy against AZT. The original trial does

not mention of the remission rates, which is an important outcome parameter in MG.[18] Subgroup analyses showed that thymectomy was not associated with an improved QMG score in males and did not lead to a significant reduction in prednisone use in patients with an age of MG onset greater than 40 years. A recent Japanese cohort study evaluated the role of thymectomy in elderly patients >65 years of age and concluded that thymectomy can be an option in elderly provided the surgery is performed within 1 year of onset of symptoms.[19] But these data come from limited number of patients and there is a need to conduct a trial to evaluate the benefit of thymectomy in patients >40 years of age.

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## Conflicts of interest

There are no conflicts of interest.

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