Improved outcomes with surgery *vs.* medical therapy in non-thymomatous myesthenia gravis: a perspective on the results of a randomized trial

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Provenance: This is a Guest Perspective commissioned by Section Editor Long Jiang (Department of Thoracic Surgery, the First Affiliated Hospital of Guangzhou Medical University, Guangzhou, China).

Comment on: Wolfe GI, Kaminski HJ, Aban IB, *et al*. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med 2016;375:511-22.

Abstract: Myasthenia gravis can be a debilitating neurological disorder that affects thousands worldwide. Thymectomy has historically been considered in patients refractory to medical therapy or with concurrent thymoma. While retrospective data and propensity matched trials have favored thymectomy in order to decrease disease severity and disease associated morbidity, no randomized data existed to clearly delineate the benefit of this practice. The reviewed paper by Wolfe *et al*. represents the first high-level randomized prospective study investigating the role of thymectomy in patients with non-thymomatous myasthenia gravis. In a subset of antibody positive patients undergoing thymectomy within 5 years of disease onset, the study demonstrated a decrease in steroid use, hospitalization and overall disease severity compared to patients receiving best medical therapy alone. This work provides a sound evidence-based foundation to strongly consider thymectomy early in the disease process, and possibly for expanded indications. Additionally, the onus lies on surgeons to identify the most efficacious and least morbid approaches to these operations, whether they be open, minimally invasive, robotic, or otherwise.

Keywords: Thymectomy; myesthenia gravis; thoracic; surgery

Submitted Nov 11, 2016. Accepted for publication Nov 21, 2016.
doi: 10.21037/atm.2016.12.54
View this article at: http://dx.doi.org/10.21037/atm.2016.12.54

Thymectomy has been a cornerstone of the treatment of myasthenia gravis (MG) but well controlled data to support this practice is sparse. Observational data shows varying levels of effectiveness of thymectomy in ameliorating MG symptoms or achieving remission of disease (1). Several large retrospective data sets indicate that there is a significant increase in achieving minimal symptoms or remission in MG patients who had a thymectomy performed (2,3). Propensity matched data also supports these findings (4). These data sets are confounded by differences in surgical technique, lack of prospective randomization and limited follow up.

Wolfe and colleagues result from the MGTX trial represent a landmark study in the treatment of MG (5). MGTX was a multicenter and international rater blinded randomized trial that began in 2006. Patients were included if they were between the ages of 18 to 60 with acetylcholine-receptor antibodies and whose Myasthenia Gravis Foundation of America clinical classification was between II and IV (between pure ocular symptoms and myasthenic crisis). Patients with disease duration greater than 3 years were initially excluded. Patients were then randomized to prednisone therapy (whether or not they were already taking prednisone or anticholinesterase

therapy) or steroid therapy and open thymectomy. Patients with thymomas were excluded. Surgeons were screened to perform open thymectomy to study standards and specimen pictures and path reports were included in the study data. In order to increase study accrual, the inclusion criteria were edited to increase the maximum disease duration to 5 years and the maximum age to 65 years old.

The primary goal of this trial was to determine the effect of thymectomy on the Quantitative Myasthenia Gravis score (MQMGS) and exposure to prednisone in patients. The results showed a significant decrease in MQMGS (2.85 points) and prednisone exposure (44 *vs.* 60 mg) in patients who had thymectomy. Secondary outcomes including requirement of immunosuppressive agents (17% *vs.* 48%), hospitalizations for MG exacerbations (9% *vs.* 37%) and likelihood of achieving minimal disease manifestations (47% *vs.* 67%) significantly favored patients who received thymectomy. As other data has shown, some of the benefit was not as profound in men. It should be noted that almost 7,000 patients were screened and 89% (5,971 patients) were excluded for disease duration greater than 5 years or age greater than 65 years old. Overall the study was well designed with good long term follow up and showed there is a clear benefit to thymectomy early in the disease process for patients with antibody positive MG.

Though this work supports the practice of thymectomy for MG in these patients, it does pose some worthwhile considerations. MG can be a challenging disease to treat and often these patients have had long term exposure to immunosuppression. Thymectomy, which has traditionally been performed through open sternotomy, is not an operation without significant technical factors. Open thymectomy for MG was first described by Blalock *et al.* over 80 years ago (6). Over this time period a number of operative approaches, including transcervical, left or right video assisted thoracoscopic surgery (VATS), sub xiphoid and robotic assisted thymectomy have evolved, all with the aim of decreasing potential morbidity in these patients (7,8).

If, as the study by Wolfe and colleagues suggest, MG is a disease in which surgical therapy is of distinct value, it is imperative that approaches to this operation strive to simultaneously maximize safety and therapeutic effectiveness. Open thymectomy requires splitting of the sternum which, though well tolerated, has a significant risk of pain, blood loss, and wound and respiratory complications. Thymectomy can also be challenging due to the density and proximity of vital structures within the operative field including the innominate vein, bilateral phrenic nerves and underlying great vessels. Additionally, for thymectomy to be maximally effective in MG, all the thymic tissue must be removed (9). Many studies have looked at minimally invasive approaches (VATS, robotic assisted) as compared to open thymectomy. Almost uniformly, these studies have found a decrease in hospital stay, ICU stay and blood loss (10-12). Differences in overall complication rates, myasthenic crisis, and cardiopulmonary complications are not as clearly determined. Most importantly, minimally invasive approaches have also been shown to demonstrably improve symptoms from MG after thymectomy (10). Comparisons between minimally invasive techniques have been limited but show comparable outcomes.

Based on the results of the study by Wolfe *et al.*, surgical therapy should clearly be considered in appropriate patients with MG. It falls to the surgical community to then more definitively determine best standards in surgical approaches to maximize therapeutic benefit and minimize patient risk. There currently is little consensus as to what this approach may be. As one example, robotic thymectomy has fast risen as a favored approach by many surgeons in this challenging patient population. While cost considerations remain a prime barrier to adoption worldwide, few would deny that the robotic approach allows for superior visualization, precision and dexterity compared to alternative approaches, ultimately providing a far greater degree of control over the conduct of operation to the operator. Also, adjunct technologies such as intraoperative near-infrared fluorescence imaging may show promise for visualizing key structures during surgery and improving the efficacy of the operation (13). However, evidence to support the translation of technical superiority provided by these sophisticated systems to improved clinical outcomes in MG is lacking. If surgery is to be increasingly considered in the care of these patients, as evidenced by Wolfe *et al.* and the MGTX trial, determining best surgical practices for thymectomy will become an increasing priority to ensure best outcomes in these patients.

Acknowledgements

None.

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Okusanya OT, Hess N, Christie N, Luketich JD, Sarkaria IS. Improved outcomes with surgery *vs.* medical therapy in non-thymomatous myesthenia gravis: a perspective on the results of a randomized trial. Ann Transl Med 2016;4(24):526. doi: 10.21037/atm.2016.12.54

