**Surgical Approaches in Myasthenia Gravis: a Systematic Review and Meta-analysis**

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**Keywords:**

**Abstract**

**Background:** Complete resection of the thymus has been shown to be beneficial in patients with myasthenia gravis (MG), but the optimal surgical approach to achieve stable remission has not been fully elucidated. This meta-analysis seeks to clarify which operative technique confers the best chance of stable remission in patients with MG.

**Methods:**

**Results:**

**Conclusion:**

**Introduction**

Myasthenia gravis is an autoimmune disease with a prevalence of 150 to 250 cases per million1. It is most commonly treated most commonly with acetylcholinesterase inhibitors, steroids, non-steroid immunosuppressive drug therapy, plasma exchange, and intravenous immunoglobulin. Approximately 21% of patients with MG have a thymoma, but 20-47% patients with thymoma have MG2,3. The thymus induces acetylcholine receptor antibody production resulting in generalized or localized weakness4. Thymectomy in patients with MG has been proposed as an effective therapy but has not until recently been shown to be beneficial5. Thymectomy for nonthymomatous myasthenia gravis (MG) was first reported in 1941 by Blalock et al. with a success rate of 50% remission of disease, and has since then been used as a surgical option for patients with medically refractory disease6. A Cochrane review in 2013 was not able to identify any rigorous randomized controlled trials confirming the benefit of thymectomy7. Since then, multiple studies have been published investigating the benefit of thymectomy as a treatment option for long-term remission of MG, showing that 40-90% of patients can achieve remission with complete thymic resection compared to only 10-20% of those on medical therapy only8. The largest multicenter trial – Thymectomy Trial in Non-Thymomatous Myasthenia Gravis Patients Receiving Prednisone (MGTX) – proved superiority of thymectomy and prednisone compared to prednisone alone at 3 and 5-year post-surgery9,10.

The surgical approach for thymectomy varies widely and the techniques described in the literature include extended transcervical thymectomy (TCT), thoracoscopic thymectomy (VATS or robotic), extended trans-sternal thymectomy, transcervical and transsternal maximal, subxiphoid thymectomy (VATS or robotic). Nevertheless, the surgical approach to thymectomy remains controversial. Minimally invasive techniques have been studied retrospectively against open approaches demonstrating a stable safety profile and feasibility as well as equivalent oncologic outcomes in patients with thymic malignancies11,12,13,14,15,16,17,18.

In this study, we aimed to clarify the effectiveness of surgical approaches for patients with myasthenia gravis focusing on long-term outcomes and complete stable remission. Specifically, we performed an extensive literature search and meta-analysis of the existing data in order to identify the optimal surgical approach for thymectomy in patients with myasthenia gravis that would have an adequate safety profile and adequate remission**.**

**Methods**

The protocol for this study is registered at PROSPERO (CRD42020166827). This manuscript is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines.

**Eligibility criteria**

We included studies comparing at least two thymectomy techniques performed in patients older than 18 years who have myasthenia gravis with or without thymoma. The outcomes of this study were complete stable remission (CSR), and pharmacological remission (PR). To minimize the risk of bias in individual studies, only publications that presented comparative cohort studies and clinical trial, limited to English language, were included.

**Data sources and searches**

A comprehensive search of several databases from each database's inception to May 6th, 2019, any language, was conducted. The databases included Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations, and Daily, Ovid EMBASE, Ovid Cochrane Central Register of Controlled Trials, Ovid Cochrane Database of Systematic Reviews, and Scopus. The search strategy was designed and conducted by an experienced librarian with input from the study's principle investigator. Controlled vocabulary supplemented with keywords was used to search for thymectomy for adults with myasthenia gravis. Conference abstracts, literature reviews, case reports and editorials we excluded. The actual strategy listing all search terms used and how they were combined is available in the appendix.

**Study selection**

Search records were uploaded into a systematic review software program (DistillerSR, Ottawa, ON, Canada). Titles and abstracts were screened by four reviewers (P.S-P., E.L-N., W.T., I.B.) separately and in duplicate, using standardized instructions. Previous abstract screening phase, a pilot was performed with 20 articles to assess which met the eligibility criteria among reviewers. Articles included by at least one reviewer were retrieved. Following this phase, eligibility of reports was considered for full-text screening. To keep tracking a match among reviewers, a pilot of 10 full-text papers were a performance. At this level, any disagreements were resolved through consensus with a third reviewer (P.S-P., E.L-N., O.J.P.) Full text screening agreement using Cohen’s kappa was (k=0.42).

**Data collection and variables**

Two reviewers (P.S-P., E.L-N) working independently and in duplicates extracted study data into a spreadsheet sheet and a third (O.J.P) checked randomly 30% of data extracted for accuracy and completeness. The variables of interest were: 1) general characteristics (author, publication date, country, study design, data collection period), 2) setting (single center, multicenter and population based-study), 3) participant baseline characteristics before surgery (age at diagnosis of myasthenia gravis, sex, signs and symptoms, antibody titers, treatments before surgery), 4) surgical approaches, 5) patients characteristics after surgery (histological types, signs and symptoms improvements, complications, operation time, and hospital length of stay ), 6) main outcomes of interest: stable complete remission (CSR) and pharmacological remission (PR), and 7) risk of bias indicators.

**Data management**

Extracted data was later classified based on different definitions. Signs and symptoms were grouped according to the Osserman score and MGFA classification. Surgical techniques were classified in three main groups to ease interpretation and comparisons among approaches….

Complete stable remission and pharmacological remission were classified according MGFA Postintervention Status. Furthermore, it was analyzed by Kaplan Meier analysis (KM) where 3-year results were either reported or could be collected from a graph; or crude cumulative “survival” analysis without KM was acceptable if all patients reported have been followed for at least 3 years (we collected also > 3 years KM and > 3 years cumulative for papers that had this data available).

**Author contact**

We decided to contact authors because the estimates of effect sizes were missing or not clear in all included articles. Additionally, an author of one study was contacted to clarify the published information. First, we retrieved first and last names, e-mails and telephone numbers of corresponding authors into a database. Second, we emailed each author asking to share the effect sizes of assessing the association of different treatment approaches with achieving complete stable remission. . If authors failed to respond in a 2-week period, we decided to contact them by sending a second e-mail. If authors did not reply after 1 week, we sent a last email. Third, only those who did not respond our e-mail contact approach were contacted by phone.

Only two authors (2/15) responded and shared their data.

**Risk of bias in individual studies**

Study quality was assessed by two independent reviewers (XXXX) based on CLARITY tool for cohort-studies and case-control studies. The domains for cohort studies are: :1) selection of exposed and non-exposed cohorts drawn from the same population; 2) assessment of exposure; 3) if our outcome of interest was not present at start of study; 4) matching exposed and unexposed for all variables that are associated with the outcome of interest or statistical adjustment for these prognostic variables; 5) assessment of the presence or absence of prognostic factors; 6) assessment of the outcome; 7) adequate follow up of cohorts; and 8) similarity of co-interventions between groups; and the domains for case-control assessment include: 1) assessment of exposure; 2) assurance that cases had developed the outcome of interest and controls had not; 3) adequate selection of cases; 4) adequate selection of controls; and 5) matching of cases and controls according to important prognostic variables or statistical adjustment for those variables.

The original responses for these questions were yes, probably yes….. Howevere, we decided to change to….

We classified the overall risk of bias based on the following criteria: 1) High risk of bias, at least one domain found at high risk of bias, 2) intermediate risk, at least two

**GRADE**

**Statistical analyses**

For time-to-event outcomes, we will follow the recommendations given by Tierney et al. First, we will convert all reported hazard ratios (HRs) into their log forms and calculate the variance (Vs) of the logHR from the reported confidence intervals and then combine them in a random effects meta-analysis. When this data is not published, we will use the observed (O) and log rank expected events (E) to calculate the corresponding hazard ratios and variances. Lastly, if only Kaplan-Meier curves are reported, we will estimate HRs and Vs of each trial by using the template published by Tierney et al. Additionally, we will calculate relative risks and their confidence intervals of each trial by using specific follow-ups. We will combine this data by using random-effects meta-analysis. The I² statistic will be used to explore heterogeneity among the included studies. Subgroup analysis will be performed for the following groups. Significance tests will be performed and reported with their corresponding p values.

Heterogeneity across studies was assessed with the I2 statistic and visually . We considered that I2 < 25% reflected low inconsistency and I2 > 75% reflected high inconsistency. In terms of subgroups analyses, predefined comparisons based on age, sex, MGFA score, Osserman score, anti-acetylcholine-receptor antibodies, were planned. The statistical program R studio was employed to perform all types of analyses and forest plots.

**Coding scripts and sharing data**

This information is found in (github)

Coding scripts and excel files with the extracted data are available online.

To convert a median to mean, we use the calculator produced by the authors of Shi 2020 and Luo 2018. Whereas, we convert range to standard deviation with the methods reported by Wan *et al*. (2014)

**Results**

The search strategy retrieved 2436 references, and 14 comparative studies were included in this systematic review. A total of 1773 patients with myasthenia gravis were enrolled in 13 cohort studies and one randomized clinical trial. Their mean age varied from 20.5 (SD 13.3) to 43.96 (SD 14.93) years, and most of the participants were female (62%). (Table 1)

Overall risk of bias ###

**Preoperative and postoperative MGFA characteristics**

According the MGFA clinical classification, most of the patients who underwent thymectomy, were in class I (21%) and class II (39%). The treatments used prior surgery were anticholinesterase treatment (25%), and steroids (21%). Moreover, 8 studies exclude population with thymoma (Table 1).

**Overall time and hospital stay by surgical approach**

The techniques with the shortest mean operative time were STsT 86.83 minutes (±27.55); VATET bi 126.8 minutes (22.2); ETsT 140.86 minutes (±46.83); and VATS uni 149.38. Whereas, those with the longest mean surgical time were VATS uni robotic 187.0 minutes (48.0); TcSxVT 181.31 minutes (42.0); and VATET uni 179.95 minutes (46.25) (Table 2)

The hospitalized length was shorter in the minimally invasive approaches (group T-2)

**Complications**

***Aggressive vs. aggressive surgical approaches***

A total of 5 studies compared aggressive vs. aggressive surgical approaches, including 531 participants. The risk of achieving stable complete remission at 3 years of follow-up was higher in patients who underwent ETsT (RR 2.84; CI: 1.47, 5.49) compared to those treated with STsT. The estimate remained consistent until 5 years of follow-up. Similarly, CSR was greater in those treated with TcSxVT compared to STsT at 3 years (RR 3.06; CI: 1.65, 5.66) to 5 years (RR 2.65; CI: 1.58, 4.45) of follow-up. However, the risk of achieving CSR was similar in patients treated with the ETsT approach compared to those treated with TcSxVT from 3 (RR #####) to 5 (RR #####) years of follow-up. At 5 years of follow-up, CSR was not different when comparing IMT to ETsT. In contrast, at 10 years of follow-up ETsT seems to increase the probability of CSR compared to BTcT.

***Less-aggressive vs. aggressive surgical approaches***

A total of 4 studies were eligible compared a less-aggressive approach with an aggressive approach and included 918 patients. The analysis of CSR shows no difference across all comparisons at different follow-ups. For instance, between VATET uni or bi versus ETsT from 3(RR 0.63; CI: 0.38, 1.04) to 8 years (RR 0.70; CI: 0.45, 1.09).And, there is not difference when VATS uni was compared with STsT and ETsT in increasing the risk of developing CSR (Fig. 2).

VATET bi vs ETsT (HR: 2.60, 95%CI 0.88-7.72)

The author from the study comparing VATS uni with ETsT shared their HR estimate (HR: 1.53, 95%CI 0.70-3.32) , which was consistent with our results.

***Less-aggressive vs. less-aggressive surgical approaches***

There are 3 studies comparing less-aggressive approaches with another similar approach, including 324 participants. In the first comparison, VATET unilateral versus bilateral, found no different on CSR from 3 (RR 1.02; CI 0.50, 2.08) to 6 years follow-up (RR 0.91; CI 0.60, 1.39). Similarly, VATS left versus right, showed no difference in achieving CSR from 3(RR 1.42; CI 0.38, 5.33) to 4 years (RR 0.71; CI 0.33, 1.51). However, when VATS uni with robotic was with VATS uni in terms of CSR, no difference was found at 3 years of follow-up (RR 1.99; CI 1.16, 3.42), but 4 years (RR 1.10; CI 0.76, 1.60).

**Discussion**

It is controversial that which surgical technique is more effective in MG. However, based on the comparative studies included in this systematic review, less invasive thymectomy approaches give similar results to more aggressive approaches. Moreover, among more aggressive approach, T3-b (Extended Trans sternal approach) seems to have better CSR in the follow-up.

The operative time was significantly shorter in the STsT.

There is no doubt that minimally invasive approaches have a shorter hospitalization time than those with more invasive approaches.