ORIGINAL ARTICLE

Early Outcomes of Simple versus Extended VATS Thymectomy in Non-Thymomatous Myasthenia Gravis; a Comparative Study

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ABSTRACT

Background: Myasthenia gravis (MG) disease affects the neuromuscular junction and leads to muscle weakness and fatigue. Thymectomy may be useful in patients with MG and the operation can be done through many different techniques, however dispute exists as to which approach and extent of excision yields the best results.
Methods: This is a prospective multi-center randomized controlled study involving 40 patients who underwent Thoracoscopic Thymectomy for management of non-thymomatous Myasthenia Gravis during the period from April 2019 to August 2020 in three tertiary hospitals. The patients were classified into two groups; group A included 20 patients that did simple VATS thymectomy and group B included 20 patients that did extended VATS thymectomy. Preoperative, operative and postoperative data were collected and analyzed to compare early results of the two techniques including AChR-Ab titre and examination of excised mediastinal fat for ectopic thymic tissue.
Results: The results showed no Intra-operative complications or conversions to an open approach in either group. The operative time was slightly longer in the extended thymectomy group but without statistical significance. The Improvement in post-op MGFA class was more pronounced in the extended group than in the simple group and is statistically significant (P=0.02). The extended thymectomy group showed more improvement in pyridostigmine and prednisone dosage compared to the simple group. The enhanced improvement in pyridostigmine dose in the extended group was statistically significant. The drop in post-op AchR-Ab titre was more in the extended group than that in the simple group, but the difference between the groups did not reach statistical significance. The extended thymectomy group showed statistically significant ($p < 0.001$) better correlation between clinical improvement and AchR-Ab levels. Patients in the extended thymectomy group stayed slightly less in hospital and had less Post-op pain but it was not of statistical significance.
Conclusion: Extended right-sided thoracoscopic thymectomy is a safe and efficient procedure which combines the benefits of extensive resection including better MGFA class with a minimally invasive approach with its benefits of less pain and improved cosmesis without added risk of complications.
Keywords: Myasthenia gravis, thoracoscopic thymectomy, simple thymectomy, extended thymectomy.

INTRODUCTION

Myasthenia gravis (MG) disease affects the neuromuscular junction and leads to muscle weakness and fatigue via acetyl-choline receptor (AChR) antibodies in 85% of the patients[1].

The thymus is a gland whose function is not limited to the gland itself, thymus cells can also be found outside the main capsule. For many years, surgical and anatomical studies showed that the thymus was frequently made of several lobes in the neck and mediastinum, often enveloped separately and not necessarily contiguous. These results suggested that removing as much of the mediastinal thymus tissue as possible might lead to treatment of non-thymomatous myasthenia gravis[3,4,5,6,7].

In the early twentieth century, occasional observations of reduced symptomatology in many myasthenic cases subjected to thyroidectomy for goiter with associated resection of the adjacent thymus, concluded a possible concomitance between the thymus and myasthenia gravis. With the remarkable advances made in the explanation and treatment of myasthenia gravis and in the anesthesic, surgical, and postoperative management of patients subjected to thoracic interventions, the high rates of morbidity and primary mortality concomitant with thymectomy have been eliminated, and thymectomy is often incorporated into a long-term management strategy for this disease[8].

Myasthenia gravis is an autoimmune disease, leading to a decrease in the available acetylcholine receptor sites at the neuromuscular junction resulting from synthesis of autoimmune antibodies that bind to these sites. It is still unclear what causes or triggers the autoimmune response[8].

Weigert[9] and Bell [10] demonstrated the concept of surgical removal of the thymus gland, and its role in the treatment of myasthenia gravis. They observed thymic malformations (hyperplasia and tumors) in autopsy in 75% of cases who died from myasthenia gravis.

Early, in 1941, Blalock[11] conducted a clinical trial with the goal of the complete removal of all thymus tissue in patients with myasthenia gravis with or without proof of a tumor, hoping to change the course of the disease. He showed the primary results in 6 of these patients who did the surgery via sternotomy [11]. There was one patient who died after surgery, this patient had severe symptoms before surgery and died of aspiration pneumonia. After a clinical follow-up for 2 to 3 months, the results showed that three of the patients had significantly improved or subsided symptoms and that the remaining two patients benefited less [8].

In 1966, a landmark report was published representing a collaborative study between the myasthenia gravis clinic at the Massachusetts General Hospital (MGH), and the Mt. Sinai Hospital myasthenia gravis clinic in New York [12]. This study included 1,355 patients with 1,013 patients alive at the time of report, 50% of whom were followed up from 5 to 15 years and 25% for more than 15 years [8]. The results of thymectomy in the female group showed striking benefit compared to medical therapy alone with 38% total remission rate and an additional 51% enhancement rate [8].

The earliest studies of the transcervical method was in early twentieth century claiming that enlarged thymus gland in infants was a prevalent cause of respiratory symptoms by airway pressure at the upper thoracic aperture. The cervical approach was generally abandoned in favour of sternotomy after Blalock's[11] report. However, there was significant morbidity and mortality concomitant with this method given that most patients had advanced myasthenic symptoms at the time of operation [8].

Anatomical research has shown wide variability in the location of thymus tissue in the cervical and anterior mediastinal region, with some microscopic foci in the fat[13,14] .

Although a century has passed since it was first proved that a thymectomy could be of value in the treatment of myasthenia gravis, controversy still exists over the choice of patients, when to think about thymectomy, what type to choose, and how to assess its benefit. To answer these questions, we need many future studies [8].

METHODS

This is a prospective multi-center randomized controlled study involving 40 patients who underwent Thoracoscopic Thymectomy for management of non-thymomatous Myasthenia Gravis during the period from April 2019 to August 2020 in 3 large tertiary hospitals with specialized chest surgery units.

The patients recruited for the study were those with non-thymomatous myasthenia gravis indicated for thymectomy. Those who were deemed unfit (MGFA class V), those on Azathioprine, and those with Thymoma were excluded.

The 40 patients were randomly assigned to one of two groups, each with 20 patients. One group underwent simple VATS Thymectomy and the other an extended VATS thymectomy.

Simple randomization was done via an online random number generator (https://numbergenerator.org).

The study aimed at Comparison of symptomatic improvement between groups as well as comparison of reduction in Medication dosage between both groups, a comparison of timing of this symptomatic improvement and reduction in medication dosage, and a comparison of preoperative and 3 months postoperative AchR antibody levels.

The prevalence of ectopic thymic tissue in mediastinal fat pathological specimens was also noted.

Full clinical assessment was done for all patients including BMI, co-morbidities, MGFA classification, and medication types and dosages. CT chest was done for all patients pre-operatively as well as routine labs and AChR-Ab titre.

AchR-Ab titre was measured using Human Acetylcholine Receptor Antibody (AChR-Ab) ELISA kit (Inova, China) (Fig. 1). Results ≥ 0.4 nmol/L were considered positive. The maximum result attainable is 0.8 nmol/L.

Operative parameters measured included operative time, complications, and ICU admission.

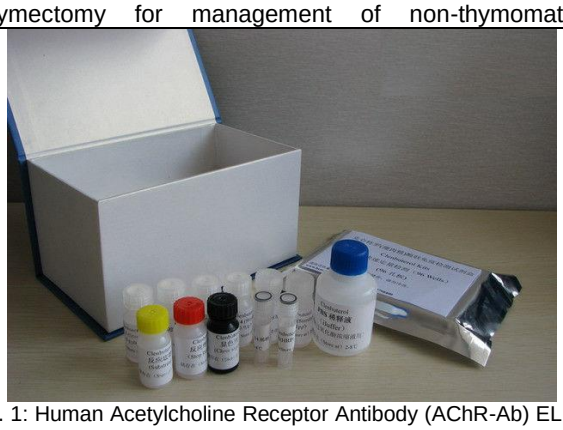


Fig. 1: Human Acetylcholine Receptor Antibody (AChR-Ab) ELISA kit (Inova, China).

Fig. 2: ENSEAL™ G2 Articulating Tissue Sealers (Ethicon Endo-Surgery, Puerto Rico, USA).

Right VATS thymectomy was routinely used in this study. After induction of general anesthesia and intubation with a single-lumen endotracheal tube, the patient is placed in the partial left lateral position with right side slightly elevated.

Three thoracic ports were used: one 10mm port was made in the 6th intercostal space at the anterior axillary line, a 2nd 5mm port was made in 3rd intercostal space at the anterior axillary line and a 3rd 10 mm port was made sub-xiphoid used as a camera port (Fig. 3).

Occasionally the subxiphoid port was not used and instead another 5mm port was inserted in the midaxillary line midway between the other two ports (Fig. 4). CO2 Insufflation was routinely used to enlarge the working space and enhance visualization.

A 30º camera was used together with a bipolar cauterization device (Fig. 2), to safely dissect the thymus

while avoiding damage to the phrenic nerves and the left innominate vein.

Thymus gland dissection often began at the lowermost part of the thymus, after identification of the right phrenic nerve. The arterial blood supply to the thymus originating from the internal mammary artery was identified and cauterized. Blunt dissection was then used to free the thymus from the contralateral pleura which was routinely opened to reduce the risk of damage to the left phrenic nerve at this point.

The left innominate vein would be visualized at this stage where dissection would continue along it until recognizing and ligating the thymic veins at their entrance into it. Dissection then proceeded above the left innominate vein with the aim of identifying and dissecting the superior horns of the thymus. The connections between the thymus and lowermost part of the thyroid gland were finally divided.

We retrieve the thymus without fragmentation using retrieval bag. Hemostasis is then done and a single chest tube is routinely placed from the right side crossing to the left pleural cavity.

In simple thymectomy only the intracapsular thymic tissue was excised. In extended thymectomy all anterior mediastinal fat from right to left phrenic nerves down to the diaphragm was excised in addition to the intracapsular thymus.

Patients were followed-up postoperatively for six months and parameters measured included postoperative complications, total hospital and ICU stay, AChR-Ab titre 3 months post-operatively, and MGFA class after 6 months.

Fig. 3: Usual arrangement of ports for right VATS thymectomy

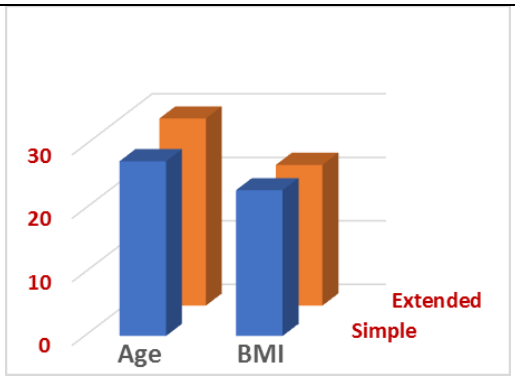
Fig. 4: Occasional arrangement of ports for right VATS thymectomy

Statistical analysis:

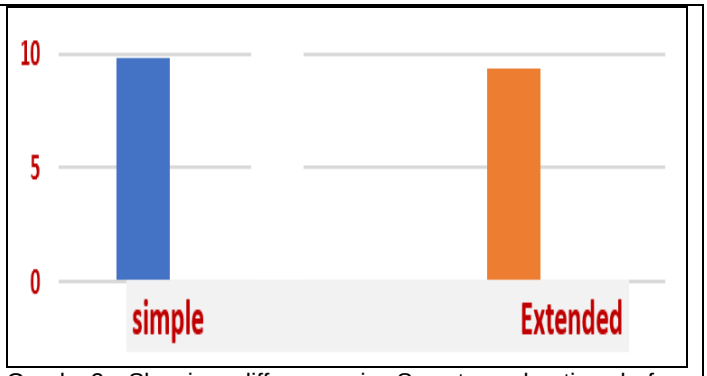
Data were abstracted by the review of clinical records and diagnostic reports. Results were then coded and entered into the statistical package SPSS (Statistical Package for the Social Sciences). Results were abstracted using mean ± standard deviation in quantitative data as well as frequency (count) and relative frequency (percentage) for categorical data. P value < 0.05 was considered significant.

RESULTS

The preoperative parameters were almost the same as there were non-significant variations in male/female ratio, age, and Body mass index (BMI). Male/Female ratio was the same in both groups, each group had 55% female and 45% male. The mean age for extended thymectomy was slightly higher (29.4±9.3 years) compared to the simple group (27.5±8.0 years) but the difference wasn't statistically significant. Body mass index (BMI) of both groups also showed no statistically significant difference.



Graph 1: Showing difference in age (years) and BMI between both groups



Graph 2: Showing difference in Symptom duration before surgery in months between both groups

Only one patient in the simple thymectomy group had an associated medical condition (Hypertension). Difference in Symptom duration before surgery between the two groups was not statistically significant.

There were no Intra-operative complications or conversions to an open approach in either group. The operative time was slightly longer in the extended thymectomy group (93 ± 21 minutes) compared to the simple thymectomy group (84 ± 30 minutes) but the difference was not statistically significant.

MGFA class distribution pre- and post-operatively in the simple and extended thymectomy groups is shown in the table (1):

The Improvement in post-op MGFA at 6 months was more pronounced in the extended group than in the simple group this difference is statistically significant {P=0.02} as shown in table (2).

The patients that saw a reduction in their medication dosage in the simple thymectomy group were 9 patients. Their pre-operative dose for pyridostigmine was 246±65 mg. Five of these patients were on prednisone with mean dose 6±2 mg. post-operatively none of the patients were on prednisone and the mean pyridostigmine dose was 193.33±73.63 mg.

In the simple thymectomy group Improvement in post-op pyridostigmine is not significant (p-value = 0.202) as was the improvement in post-op prednisone (p-value = 0.102).

In the extended thymectomy group all patients pre-operatively were on pyridostigmine with mean dose 261±76mg and 9 patients were also on prednisone with mean dose 8.12±2.42 mg. Post-operatively the mean pyridostigmine dose for all patients was 210±83.73mg and 6 patients were also on prednisone post-operatively with mean dose 8.33±5.53 mg.

Table (1): MGFA class distribution pre- and post-operatively in both groups

Class	**simple thymectomy**		**extended thymectomy**	
	Pre-operatively	**Post-operatively**	**Pre-operatively**	**Post-operatively**
No symptoms	-	15%	-	10%
class I	10%	10%	5%	10%
class IIa	15%	35%	20%	60%
class IIb	30%	15%	25%	5%
class IIIa	25%	10%	20%	5%
class IIIb	20%	5%	25%	-
class IVa	-	-	5%	-
Class V	-	10%	-	5%
Total	100%	100%	100%	100%

Table 2: Showing change in post-op MGFA at 6 months with simple and extended thymectomy:

Post-operative improvement	**Simple thymectomy**		**Extended thymectomy**	
	number	**Percentage**	**number**	**Percentage**
Improved	13	65%	16	80%
Didn't improve	5	25%	3	15%
Worsened	2	10%	1	5%

There were 10 patients that saw a reduction in their medication dosage post-operatively in the extended thymectomy group and their pre-operative dosage for pyridostigmine was 280± 79.37 mg. Five patients were also on prednisone with dose 9±2 mg. post-operatively their mean pyridostigmine dose was 180± 73.48mg and two of the patients were also on prednisone 5 mg on follow-up.

In the extended thymectomy group Improvement in post-op pyridostigmine is significant (p-value = 0.0001). However, improvement in post-op prednisone is not significant (p-value = 0.530).

Table 3: Change in post-op medications in both groups:

Medications	Simple thymectomy				Extended thymectomy			
	Pre-operatively		Post-operatively		Pre-operatively		Post-operatively	
	Pt.no	mean dosage (mg)	Pt.no	mean dosage (mg)	Pt.no	mean dosage (mg)	Pt.no	mean dosage (mg)
Pyridostigmine	11	212.73±86.38	16	195.00±80.50	11	250.91±84.08	14	192.86±71.30
Pyridostigmine +prednisone	9	260±60+ 6.67±2.36	3	270±60+ 13.75±6.49	9	273.33±67.82+ 8.12±2.42	6	270±73.48+ 8.33±5.53
Pyridostigmine +prednisone + Azathioprine	0		1		0		0	

The patients in the extended thymectomy group showed more reduction in their post-operative pyridostigmine dosage (mean dose= 113.33±20.00), than that in the simple thymectomy group (mean dose= 80±30.98). this was statistically significant (P=0.0242).

The percentage of patients showing improvement in post-op medications was more in the extended group than that in the simple group but it was with no statistical significance {P=0.71}, as showed in table (4).

Table (4): Showing Change in post-op medication dose in the simple and extended thymectomy groups:

Post-operative improvement	Simple thymectomy		Extended thymectomy	
	number	Percentage	number	Percentage
Improved	9	45%	10	50%
Didn't improve	9	45%	9	45%
worsened	2	10%	1	5%

Regarding observed change in AChR-Ab pre- and post-operatively this is seen in Table (5):

Table (5): observed change in AChR-Ab pre- and post-operatively in both groups

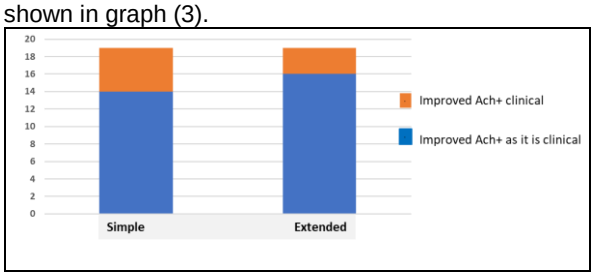
	simple thymectomy		extended thymectomy	
	Pre-operatively	Post-operatively	Pre-operatively	Post-operatively
AchR-Ab titre nmol/L	0.765±0.008	0.325±0.217	0.780±0.0615	0.325±0.177

In both groups the change was statistically significant (p-value = .00001).

Table (6): The proportion of patients showing change in AchR-Ab titre in both groups:

Post-operative improvement	Simple thymectomy		Extended thymectomy	
	number	Percentage	number	Percentage
Improved	18	90%	19	95%
Didn't improve	2	10%	1	5%
worsened	-	0%	-	0%

Regarding the correlation between AchR-Ab and clinical improvement the extended thymectomy group showed better correlation between clinical improvement and AchR-Ab levels than that of the simple operation group, this was of statistical significance {p < 0.001} as shown in graph (3).



Graph 3: Showing correlation between AChR-Ab and clinical improvement within both groups

Regarding post-operative hospital stay patients in the extended thymectomy group stayed slightly less in hospital (4.5±1.32 days) than that of the simple thymectomy patients (4.6±2.50 days), but it was not of statistical significance as P value was 0.88. Patients in the extended thymectomy group had less Post-op pain (3.2±1.24) than those in the simple thymectomy group (3.45±1.1), but it was not of statistical significance as P value was 0.50. Both simple and extended thymectomy showed approximately the same time to symptom improvement with no significant difference {P= 0.99}.

Regarding pathological analysis of extended thymectomy specimens only one showed evidence of ectopic thymic tissue. No patient in either group suffered from a surgical complication post-operatively.

DISCUSSION

Although Myasthenia gravis has been documented in the medical literature for decades and is the most well-known autoimmune neurologic disorder, still clinical trials are a challenge notwithstanding improved comprehension of pathophysiology. No randomized controlled study has been conducted that compares the results of simple and extended thoracoscopic thymectomy for non-thymomatous MG.

There were no Intra-operative complications or conversions to an open approach in either group. This is in accordance with a study by Rückert et al.[15] who compared morbidity rates for thymectomy by VATS, trans-sternal, and by anterolateral thoracotomy and found the lowest morbidity in the VATS group (5%) compared to the other 2 groups (25% and 15% respectively). Other studies by Lin et al.[16] and Chang et al.[17] comparing results of VATS thymectomy with trans-sternal thymectomy found no significant difference in morbidity between the two approaches.

The operative time was slightly longer in the extended thymectomy group (93 ± 21 minutes) compared to the simple thymectomy group (84 ± 30 minutes) but the difference was not statistically significant. The mean length of operative time corresponds to the report by Victor Tomulescu, et al. who reported a mean operative time with thoracoscopic thymectomy of 90±45 minutes [18]. Other reports as those of Shiono et al. have shown much longer operative times for thoracoscopic thymectomy (170 minutes) [19]. Others as Mantegazza et al.[20] reported shorter operative times compared to ours in the last 20 cases of their series (75.6±17.2 min) emphasising the learning curve involved in thoracoscopic approaches.

At patient follow-up after 6 months after thymectomy 16 out of the 20 patients (80%) in the extended thymectomy group showed improvement in MGFA class. These remission rates are comparable to those reported by Masaoka el at.[21] in his review of more than 380 patients (more than 280 of which had non-thymomatous MG) in which remission rates for the non-thymomatous patients after extended conventional thymectomy was 67.2% at 15 years follow-up. In this series the authors described a rise in remission rates over time which could suggest that our patients' remission rates could reach even higher numbers on long-term follow-up. Another study by Pompeo et al.[22] also showed high remission rates of 88% following thoracoscopic extended thymectomy in non-thymomatous MG patients. Another report by Okumara et al.[23] said that in their own experience, thymectomy has failed to relieve MG symptoms in only about 10% of patients.

Regarding medication dosage for control of myasthenic symptoms of the 20 patients that underwent extended thoracoscopic thymectomy 10 showed a reduction in medication dosage (50%), nine patients were taking the same medications as they did pre-operatively

and with the same dosage (45%), and only one case needed higher medication dosage than pre-operatively. This conforms with findings by Stern et al.[24] who in his retrospective study of 64 patients that underwent extended trans-sternal thymectomy with mean follow-up of 6.8 ± 0.8 years found that mean prednisone dosage reduced from 27.4 ± 4.5 mg/day preoperatively to 8.4 ± 2.2 mg/day postoperatively (P < .001). Similarly, Mestinon dosage declined from 184.7 ± 24.6 mg/day preoperatively to 76.1 ± 15.7 mg/day postoperatively (P < .001). This represents a 69.3% and 58.8% dosage reduction, respectively.

The lower rates of positive mediastinal fat specimens in our study could be attributed to presence of the ectopic thymic tissue in locations inaccessible to the right-sided thoracoscopic approach that was used in this study. This is supported by claims of Tomulescu et al.[25] who said in his study on unilateral extended thoracoscopic thymectomy using a left-sided approach that dissection of the aorto-pulmonary window and left pericardiophrenic angle is easier done from the left side as compared to a right-sided approach. The fact that those re-operated on for residual thymic tissue in this report had that residual tissue in the aorto-pulmonary window and in the contralateral cardio-phrenic angle underlines the importance of properly dissecting such areas during the thymectomy. Also, in the study done by Pompeo et al.[22] of the 18 patients that were found to have ectopic thymic tissue a third of them (6 patients) had the ectopic tissue in specimens taken from the aorto-pulmonary window or pericardiophrenic angles. It is to be mentioned however that the lack of ectopic thymic tissue in our mediastinal fat specimens did not undermine the enhanced clinical results of thoracoscopic extended thymectomy seen in our study as compared to simple thoracoscopic thymectomy. This could suggest that excision of the mediastinal fat could play a role in improvement of disease outcome through a mechanism other than removal of ectopic thymic foci.

In the extended group slightly more patients (19 out of the 20 patients) than the simple group showed reduction in AchR-Ab titre and one patient had the same AchR-Ab titre as pre-operatively. It is to be noted that a possible limitation of these results is that the test that was deployed to measure the AchR-Ab titre had a maximum result possible of 0.8 nmol/L and that all the patients that had similar pre- and post- operative AchR-Ab titres had that maximum result (0.8 nmol/L).

Regarding the relationship between clinical outcome and the measured pre- and post-operative AchR-Ab titres in our study the extended group had 16 patients (80%) showing both reduction in AchR-Ab titre and clinical improvement, while 3 patients (15%) showed only reduced AchR-Ab titre with no clinical improvement. In the report by Okamura et al.[26], in which 34 non-thymomatous myasthenic patients who underwent extended thymectomy were evaluated by comparing the pre-operative AchR-Ab titre 1 year post-operatively to pre-operative AchR-Ab titre. The report described that the typical patient's anti-AchR Ab titer decreased slowly through five years and that reduction of anti-AchR Ab titer paralleled improved symptomatology of MG.

CONCLUSION

Extended right-sided thoracoscopic thymectomy is a safe and efficient procedure which combines the benefits of extensive resection including better MGFA class with a minimally invasive approach with its benefits of less pain and improved cosmesis without added risk of complications.

AchR-Ab may correlate with post-operative clinical status especially in extended thoracoscopic thymectomy cases.

The absence of a relationship between existence of ectopic thymic foci and clinical improvement in the thoracoscopic extended thymectomy group could suggest another underlying pathogenic mechanism that is reversed when excision of the mediastinal fat is undertaken.

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