Journal of Cardiovascular Disease Research
ISSN: 0975-3583,0976-2833 VOL 15, ISSUE 9, 2024

STUDY OF PREDICTIVE FACTORS FOR PERIOPERATIVE CRISIS AND OUTCOMES AFTER THYMECTOMY

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Abstract
Introduction: Myasthenia gravis is an autoimmune disease that is charecterized by production of acetyl cholinesterase receptor auto antibodies. This is a retrospective study done in 45 patients who were offered trans-sternal thymectomy in such patients.
Objectives: Adequate pre operative preparation with immunosuppressive agents and myasthenia gravis modifying drugs, plasmapheresis before surgery helps optimize out comes.
Material and methods: Retrospectively data was collected from the years 2017-2020 in 45 patients who underwent trans-sternal thymectomy for myasthenia gravis and results analysed.
Results: There has been no mortality noted in this study. 13 patients needed post operative management of myasthenic crisis. There was no reduction in the dosage of pyridostigmine. However, there has been a significant reduction in the dosage of steroids and azathriopine.
Conclusion: Presence of thymoma, positive AChR Antibodies, moderate to severe airway disease are significant predictors of perioperative crisis. Prior adequate optimization before surgery is of utmost importance to prevent postoperative myasthenia crisis. Thymectomy is a very safe and effective procedure.

Keywords: Myasthenia gravis, Myasthenic crisis, Thymoma, Thymectomy, Plasmapheresis.

INTRODUCTION

Myasthenia gravis is an autoimmune disease characterized by the production of auto-antibodies directed against the acetylcholine receptor (AchR) of the neuromuscular synapse. Auto-antibodies directed against the AchR of the motor end plate can be detected in about 85% of all affected patients. In the remaining 15%, antibodies with specificities to other muscle targets[1](ryanodine receptor, titin) are involved, which are not detected with the standard assay. Four treatment modalities are used: anticholinesterase agents to preserve acetylcholine in the synaptic spaces, surgical thymectomy, immunosuppression, and short-term immunotherapies that include phycoerythrin and intravenous immunoglobulin. Treatments directed toward immune regulation improve functional status and reduce the risk of exacerbation. Some exacerbations, called myasthenic crisis[2], involve the respiratory muscle and are life-threatening. Myasthenic crisis occurs in 15% to 20% of patients with myasthenia gravis and is more frequent in the first 2 years of disease.[1,2]

Infections, reduction in medication, menstruation, exposure to toxic substances, emotional factors, surgery, thyroid diseases, reactions to contrast agents used with computed tomography of the chest, and the use of some medications[3] (aminoglycosides, tetracycline, muscle-relaxing agents, chloroquine, quinine, lithium, chlorpromazine, diazepam, opioids, barbiturates, corticosteroids, thyroxin, and others) are implicated in the development of crisis.

The thymus is known to play an integral part in the pathogenesis of myasthenia. The role of the thymus in the development of antibodies has been clearly established. Thymomas and glandular hyperplasia are the most common underlying pathologic findings. Hence thymectomy has become a standard procedure for managing myasthenia.

MATERIALS AND METHODS

The study was done retrospectively between 2017 and 2020 after obtaining ethics committee approval and consent from the patients and/or their attenders. 45 patients underwent trans-sternal thymectomy for myasthenia gravis at our Nizam's Institute of Medical Sciences Hospital, Hyderabad. The patients included 21 men and 24 women. Their clinical records were reviewed regarding sex, age, weight, disease duration, existence of thymoma, presence of chronic pulmonary disease (pulmonary emphysema, bronchial asthma), history of preoperative crisis, preoperative daily dose of anticholinesterase drugs, steroids and other immunosuppressive drugs, pulmonary function , serum AchR-Antibodies, operation time, intraoperative blood loss, whether patients have undergone plasmapheresis or treated with immunoglobulins, how many developed postoperative crisis, duration of postoperative hospital stay and dose modification after surgery.

Preoperative Management

The preoperative regimen of anticholinesterase therapy was maintained until the time of operation[4]. If the patient could not be stabilized with medication, then preoperative plasmapheresis was carried out. Plasmapheresis was performed for patients with acute exacerbations and myasthenic crisis[5]. Steroids(prednisone) and immunosuppressive (azathioprine) drugs were ongoing till the day of surgery.

Anaesthetic Management

Anxiolytic medications were administered. Mandatory ASA monitoring techniques were followed .Thoracic epidural catheter was inserted in the Th5-6 or Th6-7 (thoracic vertebrae) interspace. Endotracheal intubation was performed after muscle relaxation . General anesthesia was induced with thiopentone and fentanyl, and this was followed by controlled ventilation with isoflurane or sevoflurane.(MAC 1.0) was maintained using atracurium infusion.

Surgical Procedure

The surgical procedure consisted of trans-sternal thymectomy. Dissection was performed from pericardium and pleura. Pleural cavity was opened .The borders of thymectomy were the diaphragm caudally, into the neck superiorly, and phrenic nerves laterally. Three chest tubes were placed in the thoracic cavity two in each pleura and one in the mediastinum.

Postoperative Management

Analgesia was initially maintained with epidural bupivacaine (0.25%) immediately after the operation. Before the patient recovered from general anesthesia, arterial blood gas analysis was performed while the patient spontaneously breathed oxygen-enriched air (fraction of inspired oxygen, Fi_{O_2} = 0.4). Extubation was performed in the operating room or intensive care unit within 24 hours after the operation, if possible. If the patient failed to meet the criteria of extubation, mechanical ventilation was continued, plasmapheresis was reintroduced for 2-3 cycles and extubation was later performed if the criteria was met.

Definition of Myasthenic Crisis

Postoperatively all patients received chest physiotherapy, including incentive spirometry, intermittent positive-pressure breathing, aerosols, and endotracheal suctioning, if necessary. In this study, myasthenic crisis was defined as presence of occular or bulbar symptoms (dysphagia, difficulty in chewing, nasal regurgitation, slurring of speech, choking on liquids, dysarthria), respiratory weakness, postoperative reintubation or total postoperative mechanical ventilation support time of more than 48 hours with no postoperative cardiopulmonary complications. Myasthenic disorder was diagnosed by the neurologist using neuro-physiological examination and/or provocative diagnostic test using intravenous injection of edrophonium chloride (Tensilon).

Outcomes After Thymectomy

33 patients were followed up in the outpatient department and 12 by telephone calls. Outcomes were studied in terms of their clinical status improvement of myasthenia gravis or is there a dose modification in the use of steroids or anticholinesterases or immunosuppressive drugs and/or mortality if any.

Statistical Analysis

Statistical analyses were performed using SPSS 17.0 software (SPSS, Inc, Chicago, Ill). All continuous data are expressed as a mean ± standard deviation of the mean. Categorical and continuous variables were analyzed by the chi-square test (Fisher exact test) as appropriate and by an unpaired Student *t* test, respectively. Preoperative and intraoperative variables were used for the determination of statistically significant prognostic factors for perioperative myasthenic crisis. All variables were analysed in detail and correlation to the cause of myasthenia crisis and outcomes after thymectomy procedure.

RESULTS

Out of 45 patients 21 were male and 24 were female. Mean age was 42.6years. Mean duration of symptoms was 19.42 months. There were no significant differences in terms of age, sex ratio, and disease interval. 15 patients had preoperative bulbar or ocular symptoms.

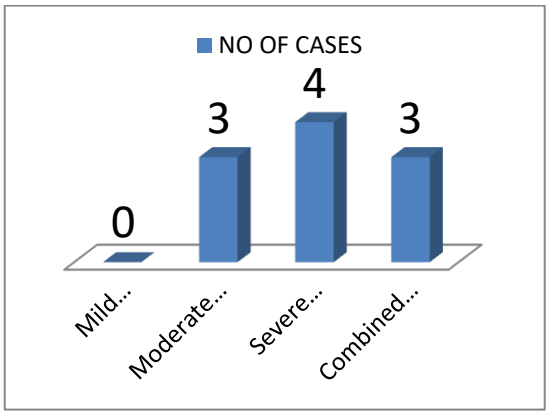
Table-1: Mean duration of symptoms and age of patients

Variables	Mean	Std. Deviation
Duration of disease	19.42	7.859
Age in years	42.6	8.907

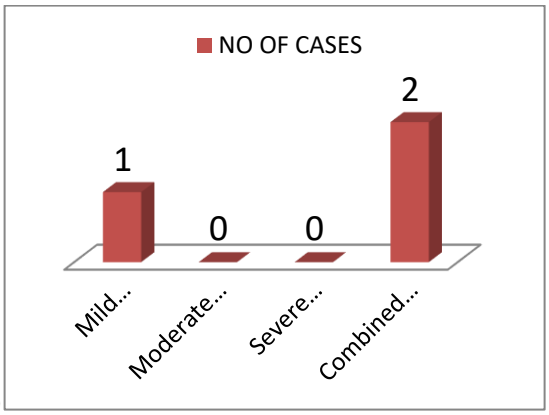
mean duration (19.42)of disease, mean age (42.60) in months

Pulmonary function

Preoperatively 14 patients had severe obstructive airway disease, 13 had moderate obstructive, 05 had mild obstructive, 09 had combined obstructive and restrictive disease, others had normal pulmonary function. Of those 13 patients who had perioperative crisis, 12 had combined, severe and moderate airway disease (p=<0.05) showing that it is statistically significant.



a)



b)

Figure 2a- shows Pulmonary function test done in patients who had preoperative crisis and **Figure 2b**-shows that in postoperative crisis.

Acetylcholine Receptor Antibodies

AchR- Ab were positive in 14 patients. They were positive in 07 patients who were in perioperative crisis (p= 0.049) showing that positive AchR Ab are significantly associated with crisis.

Table-2: shows that the association of positive acetylcholine receptor antibodies to perioperative crisis is statistically significant(p=0.049) by paired sample T test

Paired Differences				t	df	Sig. (2-tailed)
Mean	**Std. Deviation**		**95% Confidence Interval of the Difference**			

		Std. Error Mean	Lower	Upper			
Perioperative crisis - Acetylcholine Receptor Antibodies	-.956	.952	.142	-1.242	-6.730	44	.049

Operative factors

There was no significant difference with respect to operation time and amount of intraoperative blood loss . An intraoperative blood loss of > 600 mL or intraoperative blood transfusion of two or more units of blood was considered significant. Only 2 patients had significant blood loss (p=>0.05). In our study we kept operating time under 120 minutes. Anything more was considered to be significant. The procedure was done by consultant surgeons or by the residents with assistance with still the operating time being less than 120 minutes. None of the patients who went into postoperative crisis had significant operating time or bleeding.

Histopathologic Correlation

Few of the patients had preoperative diagnosis of thymoma by imaging studies. All tissue specimens were sent for histopathology. 26 had thymoma and remainder 19 had thymic hyperplasia. In those 13 patients who had crisis, thymoma was associated in 10 patients (p= 0.031) which was statistically significant.

Table-3: Shows presence of thymoma was significantly associated with perioperative crisis(p=0.031) by paired sample test.

			Presence of Thymoma	Periopcrisis
Kendall's tau_b	Presence of Thymoma	Correlation Coefficient	1.000	.315*
		Sig. (2-tailed)	.	.031
		N	46	46
	Periopcrisis	Correlation Coefficient	.315*	1.000
		Sig. (2-tailed)	.031	.
		N	46	46
Spearman's rho	Presence of Thymoma	Correlation Coefficient	1.000	.316*
		Sig. (2-tailed)	.	.032
		N	46	46
	Periopcrisis	Correlation Coefficient	.316*	1.000
		Sig. (2-tailed)	.032	.
		N	46	46

Perioperative crisis and management

Out of 45 patients 13 had perioperative crisis. All patients received plasma exchange except 2 patients who received intravenous immunoglobulins in view of suspected infection as per neurologist's advice. One patient received both IV Ig and plasmapheresis. These patients were optimally stabilized with 3 to 5 cycles of plasma exchange preoperatively depending on the symptomatic improvement. These cycles were continued postoperatively if required, to prevent crisis. Postoperatively only 3 developed crisis, 2 of which had new onset crisis due to respiratory infection and received IV Ig as mentioned above.

All our patients were adequately optimized before surgery showing that plasmapheresis is a very good and effective modality of treatment.

Outcomes

No mortality was seen after the procedure. There was no change in the dosage of anticholinesterases(pyridostigmine). However the doses of azathioprine and steroids (prednisone) were reduced post-operatively. The average doses of

prednisone and azathioprine preoperatively were 13.44 mg/day and 28.44 mg/day respectively. Postoperatively their doses were reduced to 7.44 mg/day and 10.00 mg/day respectively (p=<0.05) showing that patient compliance is effective after thymectomy and with dosage reduction of steroids and/or immunosuppressive drugs. The average duration of hospital stay was 7.33 days and those who had crisis postoperatively, had mean duration of 10.54 days.

Table-4: Shows that there is significant reduction in dosage administration of prednisone (p=0.004) and azathioprine(p=0.002) postoperatively

		N	Correlation	Sig.
Pair 1	Preoperative prednisone yes/no & postoperative prednisone yes/no	45	.426	.004
Pair 2	Preoperative azathioprine y/n & postoperative azathioprine y/n	45	.450	.002

Table-6 shows average duration of hospital stay to be 7.33 days in patients who had no myesthenic crisis and 10.54 days in patients who had crisis.

Periopcrisis		Duration of hospital stay in days
0	Mean	6.03
	N	32
	Std. Deviation	1.332
1	Mean	10.54
	N	13
	Std. Deviation	2.222
2	Mean	7.33
	N	1
	Std. Deviation	0.5
3	Mean	7.33
	N	46
	Std. Deviation	2.591

DISCUSSION

Extended thymectomy is an important approach for treating MG. However, postoperative myasthenic crisis a life-threatening complication occurs in some cases. It was defined as postoperative respiratory failure requiring prolonged ventilation support or urgent reintubation. Nevertheless, the specific threshold to diagnose postoperative myasthenic crisis has not reached consensus yet. Some studies took 24 h as the standard[3,4,], while others usually used 48 h as the criteria.[5] Surgical removal of the thymus has been an alternative treatment for this disease since Blalock et al.[6] performed a successful thymectomy in a 26-years-old woman with MG and thymus cysts. Then, Blalock et al. [6] published their study about 20 patients with MG treated with transsternal thymectomy. In the following decade, a large number of studies investigating the role of thymectomy in MG have been reported from the United States and the United Kingdom. Over time, with improvements in perioperative care, results of thymectomy have improved, and thymectomy has found its place in the treatment integrity of MG. The benefit of the thymectomy still continues to be questioned by some authors. In addition, there are still debates on the timing of thymectomy, treatment type in early ages, and surgical approaching techniques.

In our study Out of 45 patients 21 were male and 24 were female , 15 patients had preoperative bulbar or ocular symptoms. Preoperatively 14 patients had severe obstructive airway disease. Of those 13 patients who had perioperative crisis, 12 had combined, severe and moderate airway disease (p=<0.05) showing that it is statistically significant. AchR-Ab were positive in 14 patients. They were positive in 07 patients who were in perioperative crisis (p= 0.049) showing that positive AchR Ab are significantly associated with crisis. There was no significant difference with respect to operation time and amount of intraoperative blood loss . All tissue specimens were sent for histopathology. 26 had thymoma and remainder 19 had thymic hyperplasia. In those 13 patients who had crisis, thymoma was associated in 10

patients (p= 0.031) which was statistically significant. All patients received plasma exchange except 2 patients who received intravenous immunoglobulins in view of suspected infection as per neurologist's advice. No mortality was seen after the procedure. There was no change in the dosage of anticholinesterases(pyridostigmine). However the doses of azathioprine and steroids (prednisone) were reduced post-operatively. Postoperatively their doses were reduced to 7.44 mg/day and 10.00 mg/day respectively (p=<0.05) showing that patient compliance is effective after thymectomy and with dosage reduction of steroids and/or immunosuppressive drugs.

A study conducted in Japan in 2004 showed that the risk factors for myasthenic crisis after surgery were the presence of antibodies to the AChR of pre-operative, in addition to the bulbar symptoms and a history of the previous myasthenic crisis. Therefore, previous respiratory complications and symptoms are more important risk factors for the use of mechanical ventilation after surgery.[7] The ability of the patient to protect and maintain the airway permeable in the post-operative period can be compromised if the patient had a respiratory implication such as decreased ability to read and manage secretions. Ventilatory muscle strength can be quantified by pulmonary function tests (inspiratory pressure and forced vital capacity [FVC]). These tests may be necessary as a reference to determine the optimal conditions for extubation as well as the need for postoperative mechanical ventilation[8,9].

In 2016, Wolfe et al.[10] report the results of a randomized, controlled trial comparing the effects of thymectomy and prednisone therapy versus prednisone therapy alone. The results supported the benefit of thymectomy in patients with non-thymomatous MG. In the study, 126 patients with generalized AChR antibody-associated MG and less than 5 years' duration of disease (age, 16–65 years; median age, 33 years) were observed. Results were recorded by giving daily prednisone in addition to randomized extended transsternal thymectomy cases or only by giving daily prednisone . During a period of 3 years, time-dependent averaged mean quantitative MG score of thymectomy group was found to be significantly lower than of the prednisone alone group. During the 3 years, daily average prednisone-requiring was significantly lower (44 vs. 60 mg) in the thymectomy group. The proportion of immunosuppression-requiring cases by azathioprine was significantly lower in the thymectomy group (17% vs. 48%). The proportion of hospitalized patients for MG exacerbations was significantly lower in the thymectomy group (9% vs. 37%). Findings from non-randomized studies showed that thymectomy has contributed to MG remission and recovery[11,12], although before the MGTX study, usefulness of thymectomy was found to be controversial in the treatment of AChR antibody-associated MG in absence of thymoma.

Taioli et al.[13] compared conservative treatment results with thymectomy in patients with non-thymomatous MG (10.140 patients: 5,275 thymectomies, 4,865 medication) in their review in 2016. They determined that thymectomy was superior to conservative treatment with only medication in MG remission. A retrospective study conducted by Li *et al*.[5] 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. Thymectomy is recommended for patients younger than 60 years with non-thymomatous, generalized AChR antibody-associated MG. Plasmapheresis or intravenous immunoglobulin is recommended before thymectomy in patients with preoperative respiratory or bulbar symptoms.

CONCLUSION

Thymectomy is a very safe and effective procedure. Presence of thymoma, positive AChR Antibodies, moderate to severe airway disease are significant predictors of perioperative crisis. Prior adequate optimization with plasmapheresis and or immunoglobulins is of utmost importance to prevent postoperative myasthenia crisis. Also there is a significant decrease in the dosage administration of steroids (prednisone) and immunosuppresives (azathioprine) following thymectomy postoperatively.

REFERENCES

1. Changeux, J.P, Devillers-Thiery, A, and Chemouilli, P. Acetylcholine receptor (an allosteric protein) . Science.1984; 225: 1335–1345
2. Thomas, C.E, Mayer, S.A, Gungor, Y et al. Myasthenic crisis (clinical features, mortality, complications, and risk factors for prolonged intubation) . Neurology. 1997; 48: 1253–1260
3. Xue L, Wang L, Dong J, Yuan Y, Fan H, Zhang Y. et al. Risk factors of myasthenic crisis after thymectomy for thymoma patients with myasthenia gravis. *Eur J Cardiothorac Surg* 2017;52:692–7.

4. Ando T, Omasa M, Kondo T, Yamada T, Sato M, Menju T. et al. Predictive factors of myasthenic crisis after extended thymectomy for patients with myasthenia gravis. *Eur J Cardiothorac Surg* 2015;48:705–9.
5. Li K, Qian K, Feng Y, Guo W, Tan Q, Deng B.. Predictive factors of prolonged mechanical ventilation, overall survival, and quality of life in patients with post-thymectomy myasthenic crisis. *World J Surg Oncol* 2017;15:150.
6. Blalock A. Thymectomy in the treatment of myasthenia gravis: report of 20 cases. *J Thorac Surg.* 1944;13:316–39. [
7. Blichfeldt-Lauridsen L, Hansen BD. Anesthesia and myasthenia gravis. Acta Anaesthesiol Scand. 2012;56:17-22.
8. Kristensen ML, Gätke MR. The perioperative management of myasthenia gravis patients. Ugeskr Laeger. 2013;175:V05130290.
9. Xue L, Wang L, Dong J, Yuan Y, Fan H, Zhang Y, et al. Risk factors of myasthenic crisis after thymectomy for thymoma patients with myasthenia gravis. *Eur J Cardiothorac Surg.* 2017;52:692–7.
10. Wolfe GI, Kaminski HJ, Aban IB, et al. Randomized trial of thymectomy in myasthenia gravis. *N Engl J Med.* 2016;375:511–22.
11. Gronseth GS, Barohn RJ. Practice parameter: thymectomy for autoimmune myasthenia gravis (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology.* 2000;55:7–15.
12. Diaz A, Black E, Dunning J. Is thymectomy in non-thymomatous myasthenia gravis of any benefit? *Interact Cardiovasc Thorac Surg.* 2014;18:381–9.
13. Taioli E, Paschal PK, Liu B, Kaufman AJ, Flores RM. Comparison of conservative treatment and thymectomy on myasthenia gravis outcome. *Ann Thorac Surg.* 2016;102:1805–13.