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Outcome of Analysis of Thymectomy Operation In Myasthenia Gravis Patient With Or Without Adjuvant Therapy

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Abstract

Introduction: One of the autoimmune disease is Myasthenia gravis. Myasthenia gravis is an autoimmune disease characterized by a fluctuating weakness of voluntary muscles. The weakness of myasthenic patients is due to an antibody-mediated autoimmune attack against acetylcholine receptor at neuromuscular junction. Normally impulses travel down the nerve and nerve endings release a substance called acetylcholine. Acetylcholine binds or attaches to receptor on the muscle and makes the muscle contract.

Objective: To Diagnose the Myasthenia gravis patients prevent the autoimmune disease process with help of adjuvant therapy.

Materials and Methods: Study design: Cross sectional observational study. Place of study: This study was carried out in the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh. Study population: Patients diagnosed as Myasthenia Gravis admitted to the Department of Cardiac Surgery, BSMMU were selected for the criteria. Period of study: July 2018 to December 2020. Sampling method: purposive sampling. Sample Size (n): Twenty-Five (25). Grouping: Patients were divided into group: Group A: patients without plasmapheresis or immunoglobulin therapy (n=15). Group B: patients with plasmapheresis or immunoglobulin therapy, or with both plasmapheresis and immunoglobulin therapy (both Pre-Operative and Post-Operative) (n=10).

Results: In this study, twenty-five patients aged 20-50 years admitted in department of Cardiac Surgery, BSMMU who underwent Thymectomy and full filled inclusion and exclusion criteria were selected for the study Sample into two groups. Group-A (n-15) Consist of the patients who underwent thymectomy without adjuvant therapy and Group-B (n=10) consists of patients underwent thymectomy with adjuvant therapy during analysis, p-value (0.05) consider as significant. patients having thymectomy without adjuvant therapy shared lower incidence of Complication and thymectomy with adjuvant therapy of Complication more.

Conclusion: Extended thymectomy seems to be an effective treatment for MG, with low surgical morbidity. This single-centre study showed that the majority of patients benefited from the thymectomy, with tremendous clinical improvements and drug reduction post-operatively. Among 25 study subjects 10(40%) were complete remission after 12 months. Improvement and complete remission were statistically higher in without plasmapheresis/ immunoglobulin therapy or adjuvant therapy compare to patient with plasmapheresis/immunoglobulin therapy ($p<0.05$) or adjuvant therapy.

Keywords: Myasthenia gravis (MG); Autoimmune disease; Antigen; Antibody; Acetylcholine thymectomy

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Introduction

One of the autoimmune disease is Myasthenia gravis. Myasthenia gravis is an autoimmune disease characterized by a fluctuating weakness of voluntary muscles [1]. The weakness of myasthenic patients is due to an antibody-mediated autoimmune attack against acetylcholine receptor at neuromuscular junction [2]. Normally impulses travel down the nerve and nerve endings release a substance called acetylcholine. Acetylcholine binds or attaches to receptor on the muscle and makes the muscle contract. The strength of the contraction depends on how much acetylcholine the muscles receive. In myasthenia gravis, Immune system produces antibodies that block or destroy many of the receptor sites for acetylcholine in muscle. Because there are fewer receptor sites, the muscles get fewer nerve signals and become weak.in another form of MG, Immune system produces antibodies to the muscle specific tyrosine kinase protein. This also in terferes with the nerve to muscles communication and causes muscle weakness. Prevalence of myasthenia gravis approximately 10 cases per 100000 populations, it has a bimodal age distribution; young adult females and older adult of both sexes are typically affected [3]. Skeletal muscle weakness, and fatigability with repetitive activity, is characteristic. Symptoms which vary in type, severity and combination, may include: Drooping of one or both eyelid, Double or blurred vision, Weakness in arms, hands, neck, face or legs, Difficulty in chewing, smiling, swallowing or talking, Excessive fatigue in exercised muscle groups, Difficult breathing or shallow respiration [4]. I n most patients, extra ocular and eyelid muscle weakness are the first symptoms of disease. The most severe form of feature is myasthenic crisis implies failure of the muscles concerned with respiration, obstruction of the airway due to weakness of the laryngeal and pharyngeal muscles, and the accumulation of salivary and bronchial secretion [5]. The Myasthenia Gravis Foundation of America (MGFA) formed a clinical classification of the symptoms of MG [6]. This classification divides MG into 5 main classes and several subclasses, as follows. Class-I, indicating pure ocular (Any ocular weakness, may have weakness of eye closure; Strength of all other muscles is normal); Class-II indicate ocular plus other deficits (Class-II(a): Mild weakness affecting limbs ± bulbar muscles; Class-II(b): Predominantly affecting limbs ± oropharyngeal). Class-III indicate moderate generalized (Class-III (a): Moderate weakness predominantly affecting limb, axial muscles, or both; Class-III (b): Moderate generalized weakness predominantly affecting oropharyngeal, respiratory muscles, or both). Class-IV indicate severe generalized (Class-IV (a): severe weakness affecting limbs; Class-IV (b): severe weakness affecting limbs. Predominantly affects bulbar muscles). Class-V indicates Ventilator dependent except when used during routine postoperative management [7-8]. Myasthenia gravis can be difficult to diagnose because weakness is a common symptom of many disorders. Blood tests to measure AChR antibodies, about 80% of all MG patients have elevated levels of AChR antibodies that block or destroy acetylcholine receptor sites on the muscles. Tensilon test, a short-acting drug called edrophonium chloride is given intravenously. Weakness especially in the eye muscles, briefly and temporally improved, it indicates patient may have myasthenia gravis. Ice test, ice test appears to have greater sensitivity and specificity for diagnosis of ocular myasthenia [9]. Other form of investigation is nerve conduction studies/ repetitive nerve stimulation, single fiber Electromyography (EMG). Imaging includes x-ray chest posterior/anterior and lateral view, CT scan or MRI are to identify an abnormal thymus gland or a thymus gland tumour [10]. Thymoma in myasthenia gravis (MG) are neoplasm derived from thymic epithelial cells and are usually of the cortical subtype, 50% of thymoma patient developed myasthenia gravis [11]. Myasthenia gravis is associated a with various autoimmune diseases, including thyroid disease, including hashimoto's thyroiditis and graves' disease, diabetes mellitus and rheumatoid arthritis. Treatment of myasthenia gravis is by medication or surgery. Medication consist mainly acetyl cholinesterase inhibitors to directly improve muscle function and immunosuppressant drugs to reduce the autoimmune process. Thymectomy is a surgical method to treat MG. For emergency treatment, plasmapheresis or IVIG can be used as a temporary measure to remove antibodies from the blood circulation [12]. The first pharmacological choice in the treatment of MG is acetyl cholinesterase inhibitors. The second choice is immunosuppressive drugs such as azathioprine, tacrolimus [10]. Acetyl cholinesterase inhibitors can provide symptomatic benefit. Neostigmine and pyridostigmine improve muscle function; they act by slowing the normal degradation of acetylcholine at nerve endings, thereby overcoming the inhibition of the receptors. Many people with immune-mediated myasthenia are treated with immunosuppressive drugs, such as prednisone/prednisolone, cyclosporine, mycophenolate, and azathioprine. People are commonly treated with a combination of these drugs with an acetyl cholinesterase inhibitor. Treatments with some immunosuppressive take weeks to months before effects are noticed. If the myasthenia is serious (myasthenic crisis) then plasmapheresis can be used to remove the putative antibodies from the circulation. Also, intravenous immunoglobins (IVIGS) can be used to bind the circulating antibodies. Both of these treatments have relatively short-lived benefits, typically measured in weeks. Thymectomy, the surgical removal of the thymus, is essential in cases of thymoma in view of the potential neoplastic effects of the tumour [13]. The surgical approaches to the removal of the thymus. Gland include; transsternal (through the sternum), transcervical (through a small neck incision), and transthoracic (through one or both sides of the chest). With treatment, patient has a normal life expectancy except for those with a malignant thymoma [14]. Thymoma is an epithelial neoplasm of thymus, which commonly lies in anterior mediastinum. Thymomas comprise about 1% all mediastinal tumours [15]. About 10% of rnyasthenia gravis patient are found to have tumour in their thymus gland, in which case thymectomy is a very effective treatment with long term remission [16]. Thymectomy is recommended for the treatment of the myasthenia gravis. The favorable response generally occurs (2-5) years after surgery. However, the best response observed in young patients early in the course of their disease. Patients without thymoma respond well than patients with thymoma following thymectomy [17]. Among myasthenia gravis patients who suffer with severe

symptoms and sorter durations of disease, they showed greater degree of improvement after thymectomy [18]. This study will reveal the pattern of presentation, investigatory findings, treatment history, early management for thymectomy and their improvements as well as factors related to outcome following thymectomy in MG patients.

Materials and Methods

Study design

Cross sectional observational study.

Place of study

This study was carried out in the Department of Cardiac Surgery, Bangabandhu Sheikh Mujib Medical University, Dhaka, Bangladesh.

Study population

Patients diagnosed as Myasthenia Gravis admitted to the Department of Cardiac Surgery, BSMMU, Dhaka, Bangladesh.

Period of study

July 2018 to December 2020. Sampling method: purposive sampling.

Sample Size (n):

Twenty Five

Grouping:

Patients were divided into group:

- Group A: patients without plasmapheresis or immunoglobulin therapy (n=15).
- Group B: patients with plasmapheresis or immunoglobulin therapy, or with both plasmapheresis and immunoglobulin therapy (both Pre-Operative and Post-Operative) (n=10).

Selection Criteria

Inclusion criteria

- All the patients fulfilling the diagnostic criteria of MG were enrolled in the study.
- Exclusion criteria
- Bronchial asthma, pseudocholinestrase deficiency. congenital myasthenic syndrome, progressive restricted myopathies, steroid and inflammatory myopathies, motor neuron disease
- Multiple sclerosis, variant of Guillain-Barre syndrome (e.g. Miller-Fisher syndrome)
- Eaton-Lambert syndrome
- Stroke
- Drug causing myasthenia like- neuromuscular blocking agents, aminoglycosides, penicillamine, antimalarial drug, colistin, streptomycin, polymyxin B, tetracycline, organophosphate toxicity,
- Hypokalemia; hypophosphatemia

Variables

- Age
- Sex
- Duration of MG
- DM
- Hypertension
- Thyroid disorders:
- Hyperthyroid
- Hypothyroid
- Euthyroid

Symptoms

- Drooping of upper eyelid
- Double vision weakness in chewing Difficult in swallowing Slurring of speech
- Weakness in neck extension & flexion
- Weakness in upper limbs
- Weakness in lower limbs
- Generalized Weakness & fatigue Diurnal variation

Signs

- Ptosis
- Weakness of facial muscle
- Weakness of neck muscle
- Voice
- Proximal weakness of limb muscle

Treatment

- Plasmapheresis
- Intravenous immune globulin
- Surgical procedure: Extended thymectomy

Complications

Thymic crisis: Myasthenic crisis is a life-threatening condition, which is defined as weakness from acquired Myasthenia Gravis (MG) that is severe enough to necessitate intubation or to delay extubation following surgery [19]. Surgical Wound Infection: Surgical wound infection that is associated with erythema, pain, and tender, discharge, with or without associated with microbiological evidence of presence of bacteria.

Pneumonia

Radiological evidence of pulmonary shadowing associated with fever, cough, and chest pain and not explained by other pathological lesion.

Pneumothorax

Accumulation of air in pleural cavity.

Pleural effusion

Accumulation of fluid in pleural cavity

Hemorrhage

Escape of blood from the closed circuit of circulation either to interior and exterior of body.

Intravenous immune globuin:

It is known as pooled human gamma globuin or simply gamma globulin intravenous immunoglobulin (IVIG) has been prosed for the treatment of acute exacerbation of myasthenia gravis. Dose: 0.4 g/day for (5-7) days.

Surgical procedure

Extended thymectomy was performed in all cases. Standard median stermotomy had done. Thymus was identified. Phrenic naves and innominate vein identified and preserved. Blunt dissection of overlying mediastinal pleura done. Thymectomy has done along eith removal of perigalndular, periperocardial, preopleural and peridiaphragamitc pad of fat. Excised thymus was sending for histological study just after the operation, using formalin preservative.

Results

Total numbers of 25 patients were selected for study. There were two groups. Group A and Group B. Group A Considered Patients without plasmapheresis or immunoglobulin therapy. Group B considered patients with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. Among 25 patients, 15 patients were in group A and 10 patients were in group B. The findings of the study obtained from data analysis are presented below (**Table 1-9**) (**Figure 1-4**).

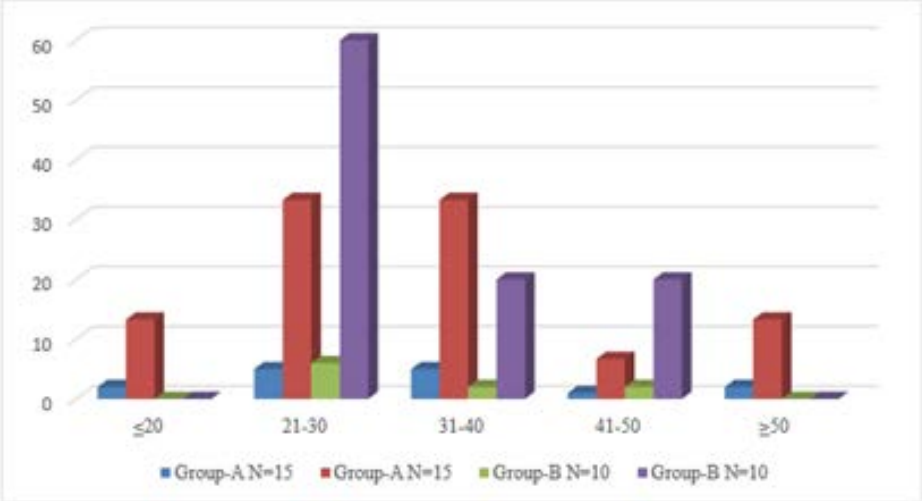

Figure 1 Comparison of age between two groups.

Table 1 Comparison of age between two group (N=25)

Sex	Group-A, N=15	Group-B, N=10	P-Value	pariso	pariso
≤ 20	2	13.3	0	0	
21-30	5	33.3	6	60	
31-40	5	33.3	2	20	
41-50	1	6.7	2	20	
≥ 50	2	13.3	0	0	
Mean ± SD	32.67 ± 11.13		27.88 ± 5.62		0.167
Minimum	17		22		
Maximum	62		37		
Date were expressed as frequency, percentage, Mean=rang. p value reached from unpaired t-test. Group A: patient without plasmapheresis or immunoglobulin therapy or adjuvant therapy. Group B: patient with plasmapheresis and / or immunoglobulin therapy or adjuvant therapy. ns: not significant. n : number of patent.					

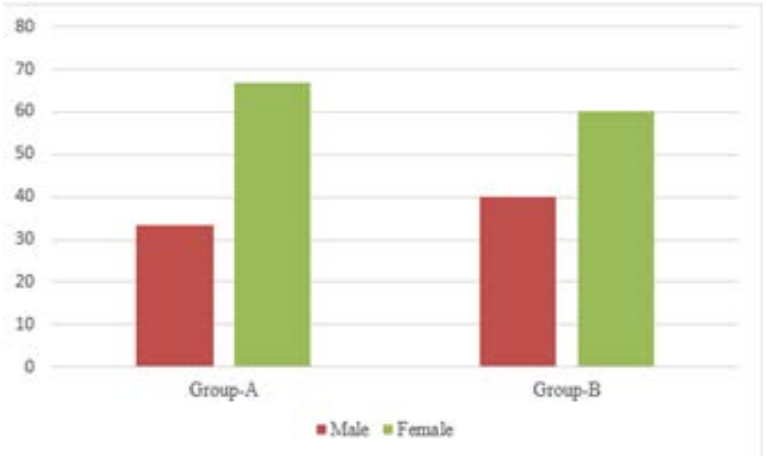

Figure 2 Sex distribution of the study subject between two groups.

Table 2 Sex distribution of the study subject between two groups (N=25)

Sex	Group-A, N=15		Group-B, N=10		P-Value
Male	5	33.3	4	40	0.534NS
Female	10	66.7	6	60	
Total	15	100	10	100	
Male: Female Ratio	01:02		01:01		
Date were expressed as frequency and percentage. P-value reached from Chi-square test. Group A: Patient without plasmapheresis or immunoglobulin therapy. Group B: patient with plasmapheresis and / or Immunoglobulin therapy. ns: not significant. n: number of patent.					

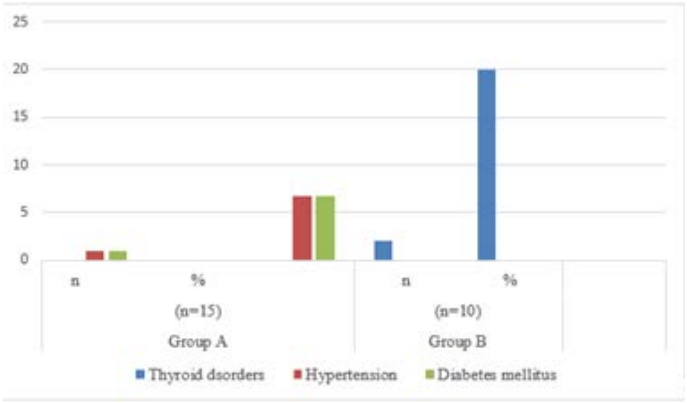

Figure 3 Distribution of the patients according to associated co-morbid.

Table 3 Distribution of the patients by duration in two groups (N=25)

Duration Of Disease	Group-A, N=15		Group-B, N=10		P-Value
<1 Years	5	33.3	4	40	0.534NS
>1 Years	10	66.7	6	60	
Total	15	100	10	100	
Data were expressed as frequency and percentage p-value reached from Chi-square test. Group A: patient without plasmapheresis or immunoglobulin therapy or adjuvant therapy. Group B: patient with plasmapheresis and / or immunoglobulin therapy or adjuvant therapy. ns : not significant , n: number of patients.					

Table 4 Comparison of age between two group (N=25)

Clinical presentation	Group-A, N=15	Group-B, N=10	P-Value	5	P-Value
Symptoms	n	%	n	%	
Drooping of eyelid	14	93.3	7	70	0.645ns
double vision	8	53.3	3	30	0.486 ns
Weakness in chewing	7	46.7	6	60	0.187 ns
difficult in swallowing	7	46.7	4	40	0.887 ns
slurring of speech	5	33.3	2	20	0.59 ns
Weakness in upper limbs	11	73.3	7	70	0.477 ns
Weakness in lower limbs	4	26.7	2	20	0.951 ns
generalized weakness and fatigue	6	40	6	60	0.122 ns
Diurnal variation	11	73.3	5	50	0.582 ns
Signptosis	14	93.3	7	70	0.646 ns
weakness of facial muscle	6	40	4	40	0.655 ns
weakness of neck muscle	1	6.7	0	0	0.465 ns
voice change	1	6.7	2	20	0.278 ns
proximal weakness of limb muscle	11	73.3	8	80	0.110 ns

Date were expressed as frequency and percentage p value reached from Chi-square test. Group A: Patient without plasmapheresis or immunoglobulin therapy or adjuvant therapy. Group B: Patient with plasmapheresis and / or immunoglobulin therapy or adjuvant therapy. ns: not significant , n: number of patients.

Table 5 Distribution of the patients according to associated co-morbid (n=25)

Associated disease	Group A, (n=15)		Group B, (n=10)		P value
	n	%	n	%	
Thyroid disorders	0	0	2	20	0.161ns
Hypertension	1	6.7	0	0	0.455ns
Diabetes mellitus	1	6.7	0	0	0.455ns

Data were expressed as frequency and percentage P-value reached from Fisher exact test. Group A: Patient without plasmapheresis of immunoglobulin therapy or adjuvant therapy. Group B: Patient with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. ns: not significant, s: Significant, n: number of patients.

Table 6 Distribution of the patients according to treatment (n=25)

Treatment	Group-A, N=15		Group-B, N=10		P-Value
	n	%	n	%	
Pyridostigmine Bromide					
Taken	14	93.33	10	100	0.498^{NS}
No Taken	1	6.67	0	0	
Neostigmine Bromide					
Taken	13	86.67	10	100	0.675^{NS}
No Taken	2	13.33	0	0	
Neostigmine Bromide					
Taken	10	66.67	8	80	0.318^{NS}
No Taken	5	33.33	2	20	
Immunosuppressant drugs					
Taken	14	93.33	8	80	0.227^{NS}
No Taken	1	6.67	2	20	

Data were expressed as frequency and percentage. P value reached from Fisher exact test. Group A: Patient without plasmapheresis of immunoglobulin therapy or adjuvant therapy. Group B: Patient with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. Ns: not significant, s: Significant, n: Number of patients.

Table 7 Distribution of the study subjects according to histopathological findings (n=25)

Histopathological findings	Group-A, N=15		Group-B, N=10		P-Value
	n	%	n	%	
Normal	3	20	3	30	6.2465
Hyperplasia	3	20	3	30	
Thymoma	9	60	4	40	

Data were expressed as frequency and percentage. P value reached from Chi-square test. Group A: Patient without plasmapheresis of immunoglobulin therapy or adjuvant therapy. Group B: Patient with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. n: not significant, s: Significant, n: number of patients.

Table 8 Distribution of the patients according to post-operative complications (n=25)

Post-operative morbidity & mortality	Group-A, N=15	Group-B, N=10	P-Value	Group-B, N=10	P-Value
	n	%	n	%	
Myasthenic crisis	0	0	1	10	0.292NS
Other	2	13.33	4	40	
Mortality	0	0	0	0	
No complication	13	86.67	5	50	

Data were expressed as frequency and percentage. P-value reached from Chi-square test. Group A: Patient without plasmapheresis of immunoglobulin therapy or adjuvant therapy.: Patient with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. ns: not significant, s: Significant, n: number of patients.

Table 9 Distribution of the study subjects according to final outcome (n=25)

Outcome	Group-A, N=15		Group-B, N=10		P-Value
	n	%	n	%	
Clinically changed					
Yes	13	86.67	6	60	0.1495
No	2	13.33	4	40	
mprovement					
Mild Improvement	1	6.67	6	60	0.0115
Moderate Improvement	4	26.66	3	30	
Significant Improvement	10	66.66	1	10	
Complete remission					
Yes	9	60	1	10	0.0175
No	6	40	9	90	

Data were expressed as frequency and percentage. P value reached from Fisher exact test. P value reached from Chi-square test. Group A: Patient without plasmapheresis of immunoglobulin therapy or adjuvant therapy. Group B: Patient with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. ns: not significant, s: Significant, n: number of patients.

Discussion

In this study both Group 25 patients were selected for study. There were two groups. Group A and Group B. Group A Considered Patients without plasmapheresis or immunoglobulin therapy. Group B considered patients with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. Among 25 patients, 15 patients were in group A and 10 patients were in group B. The relationship between MG and the thymus has been recognized for a number of years, because the thymus inpatients with MG often shows pathologic abnormalities, such as thymic follicular hyperplasia and thymic tumors. Epithelial tumor of the thymus (ie, thymoma) occurs in approximately 10% of patients with MG, and in turn, MG occurs in approximately 15% of patients with thymomas [17]. In our study Group A: Patient without plasmapheresis or immunoglobulin therapy or adjuvant therapy and Group B: Patient with plasmapheresis and/or immunoglobulin therapy or adjuvant therapy. When patients with MG also have a thymoma, their clinical manifestations are significantly distinct from those seen in the patients without thymomas. In comparison with patients without thymomas, the onset of MG in patients with thymomas tends to be late, with a peak incidence in the sixth and seventh decades, and this combined disease mostly affects men [18]. Likewise, in our practice patients with MG with thymoma were older than those without thymoma, and men were more frequently affected in the thymoma group than in the non-thymoma group Since Blalock and associates 14 reported a remission of generalized MG after removal of a thymic tumor in 1939, numerous studies have demonstrated the favorable outcomes of thymectomy on the natural course of the disease, and thymectomy is currently considered to be effective for treating MG [19]. This study in Group- A (n-15) Consist of the patients who underwent thymectomy without adjuvant therapy and Group-B (n=10) consists of patients underwent thymectomy with adjuvant therapy during analysis, p-value (0.05) consider as significant. Patients having thymectomy without adjuvant therapy shared lower incidence of Complication and thymectomy with adjuvant therapy of Complication more. Many studies have been conducted to determine the prognostic factors of thymectomy, and a variety of prognostic predictors have been identified, including age at operation, the severity of MG, and the preoperative duration of symptoms [20-22]. Among these, the presence of thymoma indicates a poor prognosis after thymectomy for MG. (3-10) Jaretzki and coworkers found a decreased remission rate and increased mortality among patients with thymomas and MG [23]. Masaoka and associates [24], in their large study of 375 patients, observed that 67.2% of the patients without thymomas achieved remission at 15 years compared with 31.8% of the patients with thymomas. They suggested that the absence of thymoma was one of the favorable prognostic factors. In our study, however, we found that patients with thymomas appeared to have better neurologic outcomes after thymectomy than did those without thymomas. However, it is still unclear how a thymoma plays a role for patients with MG, although it has been assumed that a thymoma could be the substantial source of continued antigenic stimulation. Had we performed antibody assay for various antigens other than the acetylcholine receptor, it would have been helpful to elucidate the differences between the 2 groups. In addition, because our data were retrospectively gathered and then analyzed, this study has important limitations. Further-more, the study population was rather too small to show the significant difference in neurologic outcomes between the thymoma and non thymoma groups, and there were few cases for which the relationship between relapse of MG and recurred thymoma could be investigated. If the patients had experienced recurrence of thymoma after a remission and then they had been followed by the relapse of MG, this would have been strong evidence that MG was provoked by a thymoma.

Conclusion

Extended thymectomy seems to be an effective treatment for MG, with low surgical morbidity. This single-centre study showed that the majority of patients benefited from the thymectomy, with tremendous clinical improvements and drug reduction post-operatively. Among 25 study subjects 10(40%) were complete remission after 12 months. Improvement and complete remission were statistically higher in without plasmapheresis/ immunoglobulin therapy compare to patient with plasmapheresis/ immunoglobulin therapy ($p<0.05$).

Acknowledgement

None

Conflict of Interest

None

Refernces

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