Thymectomy after Plasmapheresis in Myasthenia Gravis: 
Results of Long Term Follow up

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ABSTRACT

Background: Myasthenia gravis is the most common disorder of neuromuscular junction and several treatment modalities have been 
described for its management. Thymectomy has been employed as a treatment modality for several years. Plasmapheresis has also been 
supposed as an adjunct to thymectomy in several articles. In this study, we describe long-term results of thymectomy after plasmapheresis in 

Materials and Methods: Information related to patients was obtained from medical records. All 46 patients underwent plasmapheresis 
before thymectomy and were transferred to ICU (intensive care unit) postoperatively. The surgical approach in all patients was median 
sternotomy and complete removal of thymus gland. Long term results of surgery were obtained via calling the patients. By this manner 31 of 
46 patients were followed up.

Results: Forty-six patients including 36 women (78.3%) and 10 men (21.7%) with the mean age of 25.6±11.8 years were operated on in this 
period of time. The mean duration of symptoms was 15.7 months before the surgery. No postoperative mortality was seen. Five patients 
(10.9%) developed postoperative myasthenic crisis which was minimal in 4 of them. The mean duration of ICU stay was 18.9 hours. Thirty-
one of 46 patients were followed up with a mean duration of 7.7 years. Twelve patients (38.7%) had complete remission without using any 
drug. Twelve patients (38.7%) had significant improvement via decreasing the drug dosage necessary to control their symptoms. Two 
patients (6.4%) had no change in their disease status after the operation and in 1 patient (3.2%) with thymic pathology of invasive thymoma, 
disease worsened. Four patients (12.9%) had disease recurrence after a period of complete remission. Result of operation was more 
satisfactory in patients younger than 30 years (p<0.05%). Thymic hyperplasia foresees more favorable outcome compared to other thymic 
pathologies. The mean duration of time necessary to reach final results was 19.6 months.

Conclusion: As a result of this study, thymectomy seems to be a successful treatment modality in myasthenic patients and should be 
performed as soon as possible during the disease course. Besides, plasmapheresis has a significant role in decreasing the complications 
and improving the results of thymectomy in myasthenic patients and long term follow up is necessary for accurate evaluation of final results 
of operation. (Tanaffos 2007; 6(1): 23-28)

Key words: Myasthenia gravis, Thymectomy, Plasmapheresis
INTRODUCTION

Myasthenia gravis is the most common disorder of neuromuscular junction causing significant disabilities in affected patients (1). Several studies have been performed to introduce an effective modality with low complication rate to control this disease and its complications in a short period of time.

Acetylcholine esterase inhibitor (ACE) drugs, plasmapheresis, corticosteroids, cytotoxic agents, and intravenous immunoglobulins had different results of success and failure rate as well as side effects (1). Thymectomy as a treatment modality has been proposed in several studies and considering its effectiveness in controlling myasthenia and its complications, it was described as a successful approach.

Preoperative plasmapheresis was also the subject of several studies, some have recommended it routinely and some have advised it selectively.

In this study, we evaluate the long term results of thymectomy after routine plasmapheresis in myasthenic patients operated on in Shohada-e-Tajrish medical center from March 1996 to March 2001.

MATERIALS AND METHODS

Forty-six myasthenic patients were operated in this period of time. Their related information including age, sex, duration of symptoms, drugs, pathology of thymus, surgical complications, postoperative ICU admission, postoperative intubation time, and postoperative myasthenic crisis were obtained from their files. The diagnosis of myasthenia gravis was made in all patients based on signs and symptoms, Tensilon test, electromyography (EMG), and nerve conducting velocity (NCV) studies.

All patients tolerated plasmapheresis before the operation with a total volume of 5 to 10 liters (1 to 2 liters every other day for 5 times).

Final plasmapheresis was performed 24 to 48 hours before the operation. The surgical approach was median sternotomy and complete removal of thymus gland in all patients. The mediastinum was drained via closed suction drainage. Even when the pleura was injured during the operation, the mediastinum was drained with hemovac after repair of pleura, except for patients with large pleural defects following thymectomy because of pleural adhesions of thymus gland. In these situations the affected pleural side was drained using a 28.F thoracostomy tube. All patients were transferred to intensive care unit (ICU) postoperatively. Oral diet was started a few hours after the operation except for one patient who was intubated postoperatively because of severe myasthenic crisis. During this time, patients could not eat anything, intravenous neostigmin was prescribed and when oral feeding was started, oral mestinon was prescribed with the dosage similar to preoperative prescription. Patients were sedated using indomethacin suppositories and other non-narcotic sedatives. Intravenous cefazolin was administered for 24 hours in all patients. Patients were discharged after complete ambulation and removal of drains with the same drug dosage.

Using information recorded in patients’ files including their phone numbers and addresses, they were asked about the final results of operation. Some of patients were excluded from the study due to the fact that we were unable to contact them via phone or mail which made their follow up impossible. They were divided in 5 groups based on their long term results of operation:

2. Improvement: Control of symptoms using drug with dosage less than preoperative dosage.
3. Unchanged: No difference between pre and
postoperative disease status and drug usage.

4. Worsened (excluding postoperative crisis):
Worsening of disease and increase in drug dosage, recurrent myasthenic crisis and need for plasmapheresis and/or other treatment modalities.

5. Recurrence: Recurrence of symptoms after a period of complete remission.

RESULTS
Forty-six myasthenic patients including 36 women (78.3%) and 10 men (21.7%) were operated on from March 1996 to March 2001 in Shohada-e-Tajrish medical center. The mean age of patients was 25.6 ±11.8 yrs with an age distribution of 4-67 years. Male patients were at the age range of 15 to 40 years old with a mean age of 28.7 ± 7 years. Female patients were from 4 to 67 years with a mean age of 24.8 ±12.7 years.

Three patients (6.5%) had isolated ocular symptoms. Two patients (4.3%) had isolated bulbar symptoms. Four patients (8.7%) had ophthalmic and peripheral muscular symptoms and at last, 37 patients (80.4%) had generalized symptoms.

The mean duration of symptomatic disease before the operation was 15.7 months with a minimum of 2 weeks and maximum of 12 years.

There was no case of mortality. In 9 patients (19.6%) pleural cavity was opened, in 5 cases in the right side, in 3 cases in the left side, and in 1 case in both sides.

In 6 of 9 cases (66.7%) repair of pleura and closed suction drainage with hemovac was sufficient but in the remaining 3 cases, a 28.F thoracostomy tube was placed in pleural cavity which was removed 48 hours after the operation.

All 46 patients were extubated successfully after the operation except for one patient who was re-intubated because of severe respiratory distress.

Five patients (10.9%) developed postoperative myasthenic crisis, which was minimal in 4 of them (75%) and was controlled with short term increase of corticosteroids and anticholine esterase drugs; but in one patient (the same patient who was re-intubated) it was so severe that plasmapheresis in addition to mentioned measures was necessary.

The duration of ICU stay in operated patients was between 2 to 72 hours with a mean duration of 18.9 hours.

No case of wound infection occurred. Atelectasis occurred in 4 patients (8.7%) and urinary tract infection in one patient (2.2%) (Table.1)

Table 1. Complications of surgery.

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atelectasis</td>
<td>4</td>
<td>8.7</td>
</tr>
<tr>
<td>Wound infection</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myasthenic crisis</td>
<td>5</td>
<td>10.9%</td>
</tr>
<tr>
<td>Respiratory distress</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>1</td>
<td>2.2</td>
</tr>
<tr>
<td>Total</td>
<td>11</td>
<td>24%</td>
</tr>
</tbody>
</table>

The prescribed mestinon dose for operated patients was between 20 to 720 mg with a mean dose of 243 mg. Twelve patients (26.1%) had received corticosteroids in addition to mestinon preoperatively. All patients were discharged with a similar drug dosage to the preoperative one except for one patient who was discharged with higher dose.

The pathology of thymus gland was not found in 6 cases and in the remaining 40 patients, 31 cases of hyperplasia (77.5%), 6 cases of non-invasive thymoma (15%), one case of invasive thymoma (2.5%), and 2 cases of normal thymic tissue (5%) were reported. Thirty-one of 46 patients were successfully followed. The follow up duration was from 5.2 to 9.8 years with a mean duration of 7.7 years.

Twelve out of 31 patients (38.7%) had complete remission without using any drug, 12 cases (38.7%) had significant improvement determined by decrease
in drug dosage necessary to control their disease, 2 patients (16.4%) had no change in the disease course, in one patient (3.2%) the disease worsened and, in 4 patients (12.9%) the disease recurred after a period of complete remission of 2 years necessitating medical intervention including medications and plasmapheresis (Figure 1).

Figure 1. Final results of treatment

In patients with thymic hyperplasia the mean age was 24 years compared with 37.8 years in thymoma group with a significant difference (p=0.01). It means that thymoma patients were older than patients with hyperplasia.

Generally, the disease was more prevalent in 2nd and 3rd decades of life and these patients (<30 years) had the best results from thymectomy comparing to other groups of patients (p = 0.043) (Table 2).

Table 2. Results of surgery according to age groups.

<table>
<thead>
<tr>
<th>Age</th>
<th>Complete</th>
<th>Relative</th>
<th>Worsening</th>
<th>Recurrence</th>
<th>Unchanged</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10-19 years</td>
<td>7</td>
<td>3</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>20-29 years</td>
<td>4</td>
<td>4</td>
<td>0</td>
<td>1</td>
<td>1</td>
<td>10</td>
</tr>
<tr>
<td>30-39 years</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>0</td>
<td>6</td>
</tr>
<tr>
<td>40-49 years</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>50-60 years</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>&gt;60 years</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>12</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>31</td>
</tr>
</tbody>
</table>

Patients who had complete remission of disease after thymectomy were at the age range of 14 to 33 years with a mean age of 19.8 years and in patients who had improvement it was 11 to 67 years with a mean of 30.2 years. The difference of age between the two groups of patients was significant (p=0.04).

However, number of cases in other groups (no change, worsening and recurrence) was too small to make a valuable interpretation.

Generally, in patients older than 30 years, the result of surgery was not satisfactory.

The duration of symptomatic disease prior to the operation was between 2 weeks to 12 years with a mean duration of 15.7 months. This duration was between 2 months to 2 years with a mean of 11.5 months in patients with complete remission and between 1.5 months to 10 years with a mean of 21.1 months in patients with improvement. As mentioned above, number of patients in other groups was not adequate to perform a valuable analysis.

Although, it seems that shorter duration of disease results in better outcome, there was no significant difference between different groups of patients.

In the group of patients with thymic hyperplasia (31 patients), 22 patients were followed up, out of which 11 patients (50%) had complete remission, 8 patients (36.4%) had significant improvement and one patient (4.5%) had no change in his disease course. Disease recurrence occurred in 2 patients (9.1%) after a period of complete remission.

In non-invasive thymoma group (6 patients), 5 patients were followed up out of which no case of complete remission was noted; 3 patients (60%) had improvement of their symptoms and 2 patients (40%) had disease recurrence after a period of complete remission.

In one case of invasive thymoma the disease course was worsened after the operation.

One of 2 patients with normal thymus pathology, was followed which had no change in his disease course. However, number of cases in other groups (no change, worsening and recurrence) was too small to make a valuable interpretation.
Generally, patients with thymic pathology of hyperplasia obtain more benefit from thymectomy than patients with thymoma ($p=0.04$) (table 3).

In 31 patients followed up, 7 patients (22.6%) were male and 24 patients (77.4%) were female.

Among females, 9 patients (37.5%) had complete remission, 10 patients (41.7%) had significant improvement and 2 patients (8.3%) had no change in their disease course. In one patient (4.2%) the disease worsened after the operation and in 2 patients (8.3%) disease recurrence occurred after a period of complete remission.

Among males, 3 patients (42.8%) had complete remission, 2 patients (28.6%) had significant improvement and 2 patients (28.6%) had disease recurrence after complete remission.

In general, there was no significant difference between men and women in terms of operation results ($p>0.1$).

Considering the prevalence of thymic pathologies in two groups of males and females, the pathology report in 2 out of 10 patients showed 6 (66.7%) cases of hyperplasia and 3 (33.3%) cases of non-invasive thymoma.

Out of 37 female patients, 32 cases had pathology reports of which 26 (81.2%) had thymic hyperplasia, 3 (9.4%) had non invasive thymoma, 2 patients (6.3%) had normal thymus tissue and 1 patient (3.1%) had invasive thymoma. In summary, the thymoma is more prevalent in men ($p = 0.07$).

Time of maximum response to thymectomy after the operation, ranged from 6 months to 5 years with a mean of 19.6 months. Twelve patients had received corticosteroid preoperatively of which 10 patients were followed up. Two patients (20%) had complete remission, 7 patients (70%) had significant improvement, and 1 patient (10%) had recurrence after complete remission. As a result, corticosteroid usage had no adverse effect on results of thymectomy in myasthenic patients.

### DISCUSSION

Thymectomy as a valuable treatment modality has been used for several years in treatment of patients suffering from myasthenia gravis. There are several reports regarding the success rate of thymectomy in different studies (2-5).

In our study, 78.3% of patients were female ($f/m = 3.5/1$) which was in contrast to Western reports where the female to male ratio was 2/1 (1).

In a study in Taiwan some factors were considered to make the results of thymectomy better including: age younger than 30 years, duration of symptoms less than 24 months, and the absence of corticosteroid usage before the operation (2). In our study, the results of operation were more satisfactory in patients younger than 30 years, but disease duration and corticosteroids had no significant effect on results of operation.

In another study in Japan, it was reported that there was no difference between young and old patients in response to thymectomy (6).

In a study in Thailand it was described that women obtain more benefit from thymectomy than men (3); however, in our study there was no significant difference between men and women in this regard.

In another study in Thailand mean duration of time for maximum response reported to be 3.6 years (5). In our study, this duration of time was 19.6 months.

Preoperative plasmapheresis also was the subject
of several articles especially in recent years.

In a study in Taiwan, it was reported that preoperative plasmapheresis results in significant decrease in days of ICU stay and the total days of admission (7).

According to unofficial reports in Iran by Shohada-E-Tajrish medical center in which plasmapheresis was not performed preoperatively, postoperative mortality of 12.1% and 11.1% were reported and mean duration of ICU stay was 6.6 hours. However, in our study in the same hospital and only with the difference of preoperative plasmapheresis, mortality was 0% and mean duration of ICU stay was 18.9 hours.

As mentioned in some other studies, preoperative plasmapheresis makes the postoperative myasthenic crisis -if occurs- less severe (8, 9) which was also proved in our study.

CONCLUSIONS
Considering the results of our study we can conclude that:
1. Pathology of thymus is the most significant prognostic factor of thymectomy in myasthenic patients and hyperplasia predicts the best results.
2. Patients younger than 30 years had more satisfactory results of surgery.
3. Preoperative plasmapheresis has a significant role in decreasing the duration of ICU stay, decreasing the postoperative crisis severity and decreasing the postoperative mortality and probably improvement of final results of thymectomy.
4. Complete remission does not always mean complete cure of disease and the disease may recur. Therefore, we recommend long term follow up for all patients.
5. Final responses to thymectomy may take several months to years to be appeared and this fact again emphasizes the importance of long term follow up.
6. Thymectomy, performed with appropriate preoperative measures and meticulous surgical techniques, offers satisfactory control of myasthenia and is advisable in both sexes and all age groups.
7. Median sternotomy is an excellent surgical approach for thymectomy with a low rate of complications including wound infection and osteomyelitis.

REFERENCES

Tanaffos 2007; 6(1): 23-28