Outcome after Transsternal Radical Thymectomy for Myasthenia Gravis: 14-Year Review at Ratchaburi Hospital

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Objective : *To determine predictability factors, clinical features and outcome in the patients after transsternal radical thymectomy (TRT) for Myasthenia Gravis (MG).*

Method : *A 14- year retrospective review (1990-2004) and analysis of medical data on 32 patients with MG who underwent TRT. Two patients were lost to follow-up. Preoperative medication included anticholinesterase drugs and steroids. Plasmaphereses were used in 2 cases before operation. The modified Osserman clinical classification (Table1) was used to define disease severity. The status of the patients was evaluated as follows: A (remission), B (improvement), C (no change), D (deterioration), E (death due to myasthenia gravis). Using univariate analysis, sex, age, onset, Osserman class and pathology correlated with outcome and statistical significance is defined as $P < 0.05$.*

Results : *Among the 30 patients in the present study with MG who underwent TRT, women comprised 70% (21 of 30 patients), and mean age was 42.87 +/-12.16 year (19-65 years). The preoperative duration of the disease ranged from 0.5 to 120 months (mean = 25.72 +/-30.68 months). Clinical statuses of patients as assessed on initial evaluation were 13 patients (43.3%) were in class IIA, 6 (20%) in class IIB, and 11 (36.7%) in class III. (Table 2) The histology of thymus glands consisted of hyperplasia in 22 patients, normal in 2, atrophic thymus in 3, thymomas in 3, (2 were malignant thymomas). Hospital mortality was 0, but 9-month mortality was 3.33% (1 of 30 patients). The mean follow-up period was 41.80 +/- 53.89 months. Complete remission (A) was achieved in 40% of patients (12 of 30), and marked improvement (B) of MG in 40% (12 of 30), for a total benefit rate of 80%. 6.7% (2 of 30) were unchanged (C), 10% (3 of 30) were worse (D) and 3.3% died because of MG (E).*

Using univariate analysis on sex, clinical status by Osseman classification, and histopathology correlated significantly with outcome ($P < 0.05$); 95.2% of women (20 of 21) benefited from the procedure, versus 44.4% of men (4 of 9). 100% (19 of 19) of patients in class IIA and IIB benefited from the procedure, versus 45.5% (4 of 9) of patients in class III. All patients with thymoma presented a less favorable outcome (deteriorated in 2, and died in 1) versus 11.1% (3 of 24) of patients without thymomas were deteriorated.

Conclusion : *The remission and improvement in 80% of patients suggested that adequate thymic tissue were removed with radical thymectomy. Female, absence of thymoma, thymic hyperplasia, patients in class IIA, and IIB (non-respiratory involvement) are favorable predictability prognostic factors.*

Keywords : *Transsternal radical thymectomy, Myasthenia gravis*

J Med Assoc Thai 2004; 87(11): 1304-10
Full text. e-Journal: *http://www.medassocthai.org/journal*

Myasthenia gravis is a disease of neuromuscular transmission characterized by weakness and easy fatigability of the voluntary muscle[1]. Untreated; there is a 40% mortality rate in 10 years[2]. Surgical removal of the thymus has become an accepted and practiced therapeutic option worldwide for MG since Blalock and colleagues[3] first performed this operation in 1936. Thymectomy is recognized as an effective therapy complementing the medical management of these patients. It has been reported to result in remission or clinical

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improvement in at least 80% of patient[4]. However, These areas remain matters of controversy: 1) the selection of patients most likely to benefit from thymectomy, 2) factors predictability of response to thymectomy.

This report details our experience with treatment of MG by transsternal radical thymectomy in the past 14 years. We have analyzed clinical, predictability factors, and histological factors with respect to outcome.

Material and Method

A 14-year retrospective review (between February 1990 and April 2004) of medical data on 32 consecutive patients with MG presented with generalized muscular weakness that underwent TRT. No patient exibiting only ocular MG was subjected to thymectomy. Two patients were lost to follow-up (6.25%); the remaining 30 form the object of the present study. All patients were primarily examined and investigated by a neurologist before referral for operation.

The diagnosis was established on the basis of typical finding on neurological examination and positive response to pyridostigmine. Undiagnostic patients, confirmatory evidence was provided by a decumental response on repetitive nerve stimulation and an abnormal response on single fiber electromyography. Preoperative medication was continued until the time of surgery and readministed immediately after surgery at regular intervals. Plasmapheresis was used in 2 patients before operation and in 2 after operation.

The modified Osserman clinical classification (Table 1) was used to define disease severity.

The operative technique was similar in all patients. The thymus was approached through a full median sternotomy. Blunt and sharp dissection was performed from pericardium and pleura. The adipose tissues around the upper poles of thymus, around the innominate vein, around the aortopulmonary window, and on the pericardium (an en bloc resection of anterior mediastinal fat) were resected meticulously. The borders of resection were the diaphragm caudally, the thyroid gland cranially, and phrenic nerves laterally. Anterior pericardium was resected in one patient for grossly invasive thymoma. Postoperative radiation was used for invasive thymoma (Masaoka stage III)[5].

Following operation, all patients were managed in an intensive care unit and were maintained on mechanical ventilation until the strength of the respiratory muscles was sufficient to maintain normal blood gas exchange. All patients who had received acetyl cholinesterase inhibitors (AChEI) drug before surgery, received these agents immediately after surgery at regular intervals. After hospital discharge, the patients were followed up at regular intervals by a neurologist and a thoracic surgeon every month for medication and every one-year for remission cases.

The status of the patients post thymectomy was evaluated as follows: A (remission), B (improvement), C (no change), D (deterioration) and E (death due to myasthenia gravis) in Table 3.

Follow-up was obtained in 93.6% (30 of 32) of patients by review of hospital records, clinical records and by mail correspondence. Mean follow-up time was 41.80 $\pm$ 53.89 months, (median = 12 months)

Statistical Review

Patient preoperative data were initially set opposite outcomes, with terms of "benefit" or "no benefit" or "worse disease". Benefit means remission or improvement while no benefit means no change or deterioration or death. Statistical comparison was done using the Chi-square test and Fisher's exact test in contingency tables, with statistical significance defined as $P < 0.05$.

Results

Presentation

Twenty-one of 30 patients were female (70%) and nine were male. Their ages ranged from 19-65 years (mean 42.87+/- 12.16 years). The interval from first symptom of MG to thymectomy ranged from 0.5 to 120 months (mean 25.72+/-30.38 months). Clinical status was classified by Osserman. Distribution of numbers in each type and shown in Table 2. The histology of thymus gland consisted of hyperplasia in 22 patients, normal thymus in 2, atrophic thymus in 3, and thymoma in 3 of which two were malignant thymus as shown in Fig. 1.

Morbidity and mortality

Operative mortality was 0% but 9-month mortality was 3.33% (1of 30 patients). The mean follow up time was 41.80 +/-53.89 months. The complication rate was 20% (6 of 30); 3 patients had perioperative pneumonia. Other complications were urinary tract

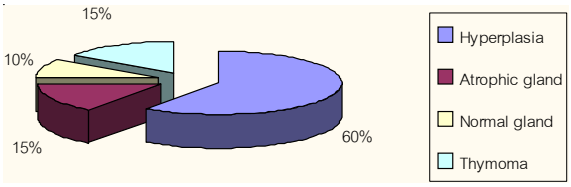

Fig. 1 Histology of thymus gland in thymectomied patients

Table 1. Clinical Classification of Myasthenia Gravis, After Osserman

Group	Muscle Involvement
I. Ocular	Ocular only, ptosis, diplopia
II. Generalised	
A. Mild	Ocular frequent, gradual spread to skeletal and bulbar No respiratory involvement
B. Moderate	Frequent ocular, gradual onset, more severe skeletal and bulbar Some dysarthria, dysphasia and mastication problems No respiratory involvement
III. Acute fulminating	Rapid onset, severe bulbar and skeletal Early respiratory involvement High percentage of thymomas
IV. Late severe	Severe symptoms about two years after most Group II symptoms

Table 2. Clinical status and number of patients

Clinical status (class)	Number of Patients
II A	13 (43.33%)
II B	6 (20.00%)
III	11 (36.67%)

Table 3. The status of the patients post thymectomy

A (Remission)	=	medical treatment could be totally withdrawn > 3 months, off all AChEI
B (Improvement)	=	decreased AchEI, improved clinical status
C (No change)	=	not change in medication, have a stable disease
D (Deterioration)	=	No muscular improvement, required more AchEI
E	=	Death due to myasthenia gravis

infection in 1, GI bleeding in 1, sternal infection with MRSA +ve S. aureus in 1 patient (Table 4, 5).

The average length of stay (LOS) was 10 +/- 2.16 days in patients without complication but LOS was increased in patients with complications to 43 +/ -37.62 days P < 0.005 (S).

Outcome

Symptomatic response to thymectomy was obtained in 30 patients, mean follow up time was 41.80 +/- 53.89 months, (median = 12 months). There was 40% rate of complete remission (A) (12 of 30), and 40% (B) (12 of 30) of patients improved. The percentage of

Table 4. Morbidity and mortality

Morbidity and mortality	Patients number (%)
Complication	6 (20%)
Perioperative pneumonia	3
GI hemorrhage (from steroid induced gastritis)	1
UTI (E. coli)	1
Sternal wound infection (MRSA + ve S. aureus)	1
Death	
In hospital mortality	0
9-month mortality	1 (3.33%)
Cause Myasthenic crisis Dead 2 hrs after plasmapheresis	

Table 5. Complication with perioperative pneumonia

Complication	Patients (n)	LOS (days)
Acenetobactor buemanni	2	(21,45)
Mixed infect with Serratia marcescens (pre-operative infection) Pseudomonas aeroginosa and Acenetobactor buemanni (post-operative infection)	1	64

patients benefiting from TST was therefore 80% (24 of 30), 6.2% (2 of 30) were no change (C), 10% (3 of 30) were worse (D) and 3.3% (1 of 30) died. The outcome of TST in relation to predicting factors is listed in Table 6.

Predictors of outcome

Sex correlated with outcome in the univariate analysis. Female MG patients significantly benefited from TST, with 95.2% (20 of 21) in remission or improved while 55.36% of men (5 of 9) and 4.8% (1 of 21) of women did not, (P = 0.005).

Patient age in the present study correlated with outcome. Myasthenic patients younger than 51 were more likely, but the difference was not statistically significant, to benefit from TST than those older than 50 (81% or 17 of 21 versus 77.8% or 7 of 9) P = 1.000 (NS).

Preoperative symptom duration did not correlate with outcome from TST. The duration less than or equal to 12 months did not significantly benefit from TST than the duration more than 12 months (80% or 12 of 15 versus 80% or 12 of 15). This is in contrast to the findings of many other studies. P = 1.000 (NS). In detail, complete remission was found in 58.33% (7 of 12) with a short duration of symptoms less than or

Table 6. Outcome of TRT in relation to sex, onset clinical status and to pathological finding

Result of operation	Number of patients (Female, Male)	Number of patients by duration in month < = 12 or > 12 months		Number of patients by clinical status			Number of patients by histopathology finding			
				IIA	IIB	III	H	N	A	T
A Remission	12(11,1)	7	5	9	3		8	1	2	
B Improvement	12(9,3)	5	7	4	3	5	12		1	
C No change	2(0,2)	2				2	1			1
D Deterioration or worse	3(1,2)	1	2			3	1	1		1*
E Death	1(0,1)		1			1				1*
Total	30(21,9)	15	15	13	6	11	22	2	3	3

H = Thymic hyperplasia, N = Normal Thymus gland, A = Atrophy, T = Thymoma (* Malignant thymoma)

equal to 12 months. Unfavorable result with deterioration and death was found in 20% (3 of 15) with a longer duration than 12 months versus 6.67% (1 of 13) with a short duration less than or equal to 12 months (Table 6).

Modified Osserman classification correlated with outcome, patients in class IIA and IIB tended to benefit more than classIII (100% or 19 of 19 versus 45.5% or 5 of 9) P = 0.001(S) from TST, (Fig. 2). There was no patient in class 0 and 4 to compare with other classes in the present series. Because of a small number of histological findings, the authors reported the outcome by univariate analysis between thymoma, nonthymoma, hyperplasic and atrophic thymus gland (Fig. 3.1, 3.2).

In the present study 90.9% (20 of 22) of patients with hyperplastic thymus glands achieved remission or improvement, compared with 50% (4 of 8) of those without hyperplatic thymus gland (normal, atrophic and thymoma) P = 0.029. A significantly high percentage of patients with thymoma responded poorly to TRT (0%, 0 of 3), P = 0.005. The patient variable listed in Table 7 was recorded and examined for correlation with each other and with outcome.

Discussion

The presented data confirmed the finding of others[6] that thymectomy can be carried out in patients with MG with low morbidity and mortality rates and an 80% of clinical improvement. The complete remission rate 40% may not be comparable to the other series in Table 8 due to different surgical criteria surgical approach and in patient selection[7,8] the authors prefer TST for both thymomatous and nonthymomutous MG because of allowing removal of ectopic foci of thymic tissue lying in the mediastinum. Trancervical thymectomy may result in incomplete resection. The rate of reoperation of ectopic thymic remnant following this approach has been reported at 27%. Video assisted thoracoscopic thymectomy (VATS) is a minimal invasive technique for thymectomy, which may result in complete resection in some areas such as diaphragmatic surface, aortocaval groove, posterior to innominate vein, and aortopulmonary window. The clinical remission was achieved in 26%[9]. A result of VATS thymectomy must be followed in long term period.

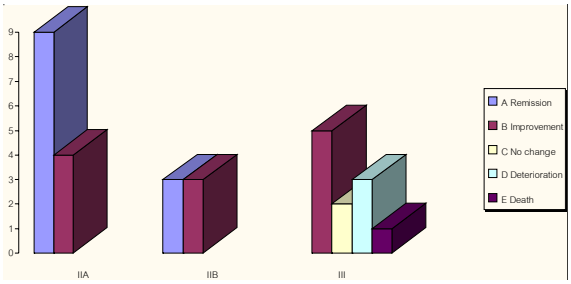

Fig. 2 Number of patient by clinical status correlated with outcome

The authors obtained a significant improvement result in female patients, 95.2% versus 44.4% in male patients (P = 0.05). The remission rate in females was 50%; the male patients often had a poorer response, 55.6% versus 4.8%. Many studies have found improved outcome in female patients[10,11]. Age at the time of thymectomy has shown a correlation with outcome. A study by Masaoka[12] found better outcome in younger patients, which was similar to others[12-14]. In the present study, the authors found a similar trend but statistical analysis was non significant (P = 1.000) complication rate was not higher in those older than 50 years, with 9 months mortality of 3.33% (1 of 30) patients from myasthenia crisis after plasmapheresis.

Patients with a shorter duration of symptoms before the operation (< 12 months) obtained a similar outcome as patients with a duration > 12 months, P = 1.000. This finding was different from other series[15]. In the present study 58.33% of complete remission was found in patients with a short duration of symptoms

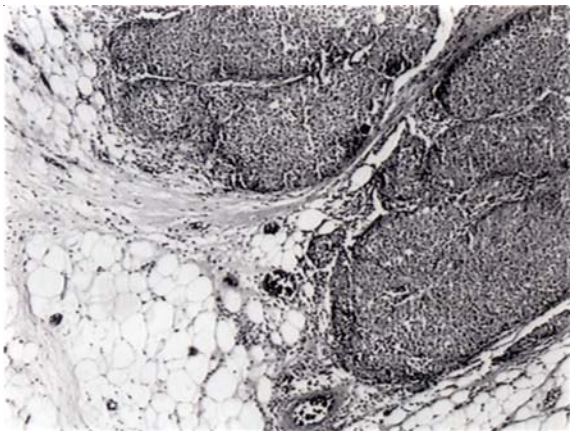

Fig. 3.1 Poor prognostic malignant thymoma with invasion to mediastinal fat

Fig. 3.2 The most common histology of lymphoid follicular hyperplasia with active germinal center

Table 7. Preoperative variables and associations with outcomes

Patient variable	Outcome	P-value		Fisher's Exact Test
Sex				
Male	Worse disease	0.05	S	10.15
Female	Remission or improvement	0.05	S	10.15
Modified	Osserman			
Class IIA IIB	Remission or improvement	0.01	S	12.955
Class III	Worse disease	0.01	S	12.955
Pathology				
Hyperplasia	Remission or Improvement	0.029	S	6.136
Thymoma	Worse disease	0.05	S	13.333
Normal thymus gland	Remission or Improvement	0.366	NS	1.205
Atrophy	Remission or Improvement	1.00	NS	0.833
Length of time of preoperative symptom				
< 12 months	Remission or Improvement	1.00	NS	0.000
>12 months	Worse disease	1.00	NS	0.000
Age				
< 50 years	Remission or improvement	0.6	NS	0.040
> 50 years	Worse disease	0.6	NS	0.040

Benefit mean remission or improvement. No benefit mean worse disease, deterioration or death.
S =significant; NS= not significant

Table 8. Comparison of Outcome in Studies That Examined Role of Thymectomy in Myasthenia Gravis

Author (Ref.)	n	Remission (%)	Improvement (%)	Follow-up (Years)
Oosterhuis[16] N*	73	22	34	15.3
Masaoka et al[12] TRT	375	47	42	20.0
Bril et al[17] CT	52	44	46	8.4
Budde JM et al[14] LS	113	21	54	4.3
Federio et al[15] CL,LS	217	25	46	9.9
Chanin et al (present) TRT	30	40	40	3.5

N* = Non operative study, TRT= Transsternal radical thymectomy or Extended thymectomy, CT= Trancervical thymectomy, LS = Limited upper transsternal thymectomy

(0.5, 4, 6, 12, 12, 12 and 12 months) and 41.66% found in those with a long duration of symptoms (24, 24, 36, 96 and 120 months) respectively.

Conclusion

In summary, the present review of 30 myasthenia patients undergoing transsternal radical thymectomy shows a remission rate and improvement in 80% similar to other studies[4,15]. The improvement in the majority of patients suggested that adequate thymic tissue was removed by this type of operation. Female sex, absence of thymoma, thymic hyperplasia, patients in class IIA and IIB (non respiratory involvement) were favorable prognostic factors. These factors

were found to correlate statistically with outcomes, which should assist in decision-making in high-risk patients.

Acknowledgements

The authors wish to thank Dr.Suthep Choojai MD, staff of Thoracic Surgery, Ratchaburi Hospital for surgical consultation and improving the English language presentation of the manuscript. The authors also wish to thank Mr. Suthisan Wattanamano MSc, (Public Health) for his help with the statistics.

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การผ่าตัดต่อมไธมัสแบบแรดดิเคิลผ่านกระดูกหน้าอกรักษาโรคไมแอสทีเนียเกรวิส: ประสบการณ์ 14 ปีในโรงพยาบาลราชบุรี

ชนินทร์ กลิ่นจงกล, ศุภชัย ไพบูลย์ผล

ระยะเวลา 14 ปี ระหว่างเดือนกุมภาพันธ์ 2533 ถึงเดือนเมษายน 2547 ได้ทำการผ่าตัดต่อมไธมัส (Transternal radical thymectomy) จำนวน 32 ราย ติดตามผลการรักษาได้ 30 ราย พบว่าเป็นเพศหญิง 70% 21 ราย ใน 30 รายอายุเฉลี่ย 42.87+/-12.16 ปี (19-65 ปี) ระยะเวลาที่แสดงอาการก่อนผ่าตัด 0.5-120 เดือน จำแนกความรุนแรงของโรคตาม Osserman Classification เป็นกลุ่ม IIA 13 ราย (43.3%) ,IIB 6 ราย (20%) และ III 11 ราย (36.7%) ผลชิ้นเนื้อเป็น hyperplasia 22 ราย ไธมัสปกติ 2 ราย atrophic thymus 3 ราย และเป็นเนื้องอก thymoma 3 ราย ไม่พบอัตราการตายหลังผ่าตัดในโรงพยาบาล มี 1 รายเสียชีวิต 9 เดือน จากโรคและเป็นมะเร็งของไธมัส ระยะเวลาติดตามผลการรักษา 41.80+/-53.89 เดือน ผู้ป่วยหายขาด 40% ลดขนาดยาลง 40% ได้ประโยชน์จากการผ่าตัด 80% ผลการรักษาคงเดิม 2 ราย (6.7%) เลวลง 3 ราย (10%) และเสียชีวิต 1 ราย (3.3%)

การวิเคราะห์ข้อมูลพบว่า เพศหญิงดีกว่าเพศชาย ผู้ป่วยกลุ่ม IIA และกลุ่ม IIB ที่ไม่มีการหายใจผิดปกติได้ผลดีกว่ากลุ่ม III รายที่เป็นเนื้องอกต่อมไธมัส (thymoma) มีพยากรณ์โรคที่เลวลงกว่ากลุ่ม hyperplasia อย่างมีนัยสำคัญ $P < 0.05$ และผู้ป่วยได้รับประโยชน์จากการผ่าตัดวิธีนี้ประมาณ 80% อัตราตายต่ำ ข้อมูลที่ได้จากการศึกษาครั้งนี้น่าจะมีประโยชน์ในการผ่าตัดในผู้ป่วยที่มีอัตราเสี่ยงสูง