A Randomized Control Study on the Efficacy of Thymectomy in Patients with Nonthymomatous (without Chest Tumor) Myasthenia Gravis

Dear editor,

Myasthenia gravis (MG) is a chronic disease with deficits in neuromuscular junctions' transmission. It has been estimated that at least 300,000 people are suffering from MG in China, but most of them are children and young adults.[1] MG may affect any skeletal muscle and muscles that control eye and eyelid movement, facial expression, and swallowing, thus seriously affecting the daily life and learning ability of patients, with a risk of death.[2]

The efficient treatment for MG is thymectomy, which is a long-standing problem that plagues surgical modality of treatment. Although the Myasthenia Gravis Foundation of America (MGFA) has announced a well-established assessment for MG treatment,[3] the therapeutic role of surgery in MG remains controversial due to the lack of the prospective randomized controlled trials in patients with MG. At present, the main confusions in the MG treatment are focusing on the following question: the choice of treatment for patients with generalized myasthenia gravis (GMG) without tumor between surgery plus drug treatment or simple immunotherapy.[4] A systematic review of articles describing outcomes in 21 cohorts of patients with MG did point out numerous methodologic flaws that prevented definite conclusions to be drawn regarding the benefits of thymectomy in patients with nonthymomatous MG.[5]

Numerous retrospective studies have shown that most surgeons considered thymectomy as the favorable treatment for MG,[6-9] suggesting that surgical treatment was superior to other conservative therapies.[10] However, due to wrong descriptors, the effectiveness of thymectomy for MG treatment cannot be extensively agreed. In contrast, the neurologists and thoracic surgeons hold a different argument that thymectomy could not completely eliminate the antibodies which were produced not only in the thymic lymphocytes but also from extrathymus tissue, leaving the immune disorder of MG untreated.[11,12] This might be the reason why the efficacy of thymectomy for patients with MG varies, and thus the underlying mechanisms remain to be discovered.

This study aims to compare the overall efficacy of two treatments for nonthymomatous MG patients: drug care only and surgical thymectomy combined with drug care. The time-dependent follow-up studies after the treatments for MG patients were also conducted.

In this study, 54 nontumor MG patients were recruited from Huashan Hospital of Fudan University between 2015 and 2017. Table S1 summarizes the clinical characteristics of these patients. A consort flow diagram was also given to describe the procedures for this study [Figure 1]. All the patients were randomly divided into two groups: (1) 25 patients with MG were only treated with bromopyridinium (or pyridostigmine bromide) 180–240 mg daily (group M) and (2) 29 patients with MG were treated with both drugs and thymectomy (group SM). Detailed guidelines for drug receiving and surgery are described in supplementary material.

The median age of group SM patients at onset was 27.48 ± 7.48 years and for group M patients was 46.69 ± 16.48 years. After a randomized, double-blind trial, we found that no significant difference was identified in age, gender, primary symptoms, initial duration of the symptom, Osserman score, and MGFA score at first diagnosis.

To quantitatively compare the severity of symptoms for group SM and group M patients at diagnosis and 3, 6, 9, 12, and 15 months after diagnosis, Quautitative myasthenia score (QMGScore) publishedby Myasthenia Gravis Foundation of America (MGFA), manual muscle testing (MMT)-Cranial nerves score, MMT-organism score, total MMT score, and activities of daily living (ADL) score tests score were used.

In MGFA-QMG score [Table S2], the results showed that the severity score in group M patients at diagnosis was slightly higher than that in group SM patients, but no significant difference was detected. However, starting from 3 months after diagnosis, the severity of all the patients in group M was higher than that in group SM patients, with most significant difference in 15 months [6.17 ± 4.3 vs. 2.28 ± 1.81, $P1 < 0.001$; Table S2]. To compare the difference between two groups at diagnosis, the differences in group M and group SM at 3–15 months after diagnosis were compared with that at diagnosis. No significant difference was identified for this comparison. In addition, for repeated measurement data analysis, random effect model (or panel regression model) was used to analyze the interaction of time-grouping factors, and the results showed that there was no statistical difference in the slope between the two groups ($P = 0.160$).

In MMT-Cranial nerves score [Table S3], the results showed that the severity score in group M patients at diagnosis was significantly higher than that in group SM patients. Similarly, the severity of all the patients in group M except at 15 months was higher than that in group SM patients. To compare the difference between two groups at diagnosis, the differences in group M and group SM at 3–15 months after

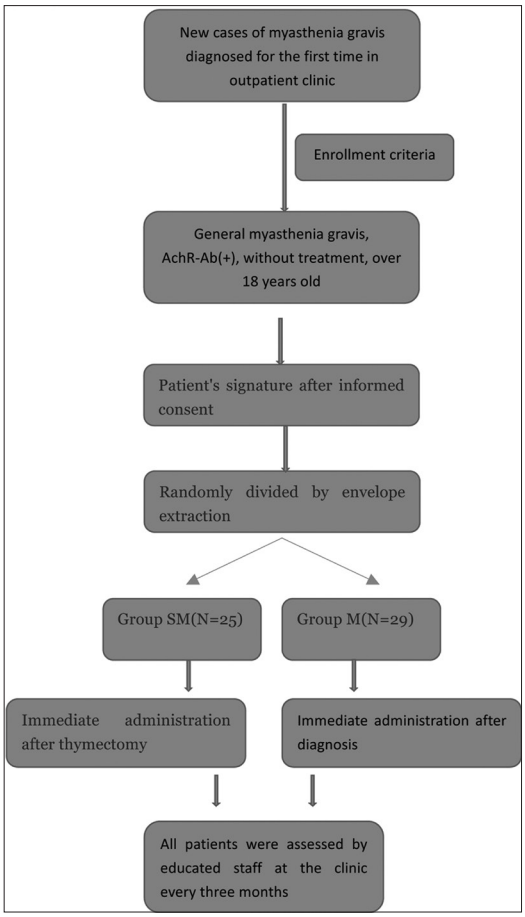

Figure 1: Consort flow diagram of the study

diagnosis were compared with that at diagnosis. Only after 12 or 15 months, there existed significant difference when compared with that at diagnosis ($P2 < 0.05$, respectively). For repeated measurement data analysis, random effect model showed that the residual was skewed with an intercept of 0.6496, and there was a statistical difference in the slope between the two groups ($P = 0.007$), indicating the changes in group SM were significantly higher than that in group SM.

In MMT-organism score [Table S4], the results showed that there was no difference in severity score for group M and group SM patients at diagnosis. However, it was hard to find significant difference between the two groups except at 3 and 12 months after diagnosis (3.84 ± 4.88 vs. 9.14 ± 9.88, $P1 < 0.05$; 1.4 ± 2.29 vs. 4.83 ± 7.33, $P1 < 0.05$). No significant difference was identified when the scores of group M and group SM at 3–15 months after diagnosis were compared with that at diagnosis. For repeated measurement data analysis, random effect model showed that the residual was skewed, but there was no difference in slope between the two groups ($P = 0.158$).

In total MMT score [Table S5], a significant difference was showed for group M and group SM patients at diagnosis (13.04 ± 8.66 vs. 22.14 ± 14, $P1 < 0.01$). Also, there were significant differences between the two groups except at 6 and 15 months after diagnosis ($P1 < 0.05$). The significant difference was only identified when the scores of group M and group SM at 15 months after diagnosis were compared with that at diagnosis ($P2 < 0.05$). For repeated measurement data analysis, it showed that the residual was skewed and significant difference was identified in slope between the two groups ($P = 0.009$), suggesting that the changes in total MMT score of group SM were higher than that in group M.

In standardized ADL score [Table S6], no difference was showed for group M and group SM patients at diagnosis. However, there existed significant differences between the two groups at 9 and 15 months after diagnosis (1.4 ± 1.89 vs. 2.76 ± 2.69, $P1 < 0.05$; 0.56 ± 0.87 vs. 2.31 ± 3.15, $P1 < 0.05$). No difference was identified when the scores of group M and group SM were compared with that at diagnosis. Also, no difference was identified in slope between the two groups with repeated measurement data analysis.

In MG-QOL-15 [Table S7], no difference was detected for group M and group SM patients at diagnosis. But there were significant differences between the two groups except at each time point except at 3 months after diagnosis. When the scores of group M and group SM at 15 months after diagnosis were compared with that at diagnosis, the only significant difference was found at 9 and 15 months ($P2 < 0.05$). For repeated measurement data analysis, no difference was identified in slope between the two groups ($P = 0.009$).

MG is an autoimmune disease that is mediated by binding autoimmune antibodies to the nicotinic acetylcholine receptor in skeletal muscle at the neuromuscular junction. The efficiency of clinic treatment needs a long time to be observed. In this study, we set 3 months as follow-up intervals to evaluate in the outpatient clinic. Group SM patients were evaluated with four different indicators. Osserman and MGFA scores were used to assess the progression of MG and whether the disease was worsened. The results showed that the progression of the MG in group SM (0.0%) was slower than that in group M (13.8%). There was no statistical difference between the two groups with regard to the risk of occurrence and deterioration rate [Table S8].

In a report given by the Quality Standards Subcommittee of the American Academy of Neurology, the following characteristics from controlled studies were abstracted: method and setting of cohort assembly, years during which patients were enrolled in the cohort, number of subjects assembled, duration of follow-up, proportion of subjects lost to follow-up, and the thymectomy techniques used.[5] Gronseth and Barohn and Skeie *et al*.[5,13] screened 28 cases on the efficacy on thymectomy from 1953 to 1998 and studied the correlations between age, gender, disease duration, and MG grades with meta analysis, which indicated that thymectomy has a significant effect on the treatment of MG (18/21). Surprisingly, the analysis showed

that patients with MG with ocular muscles and mild GMG did not benefit from thymectomy, and the surgical outcome did not differ between young and elder patients, suggesting that thymectomy has a great potential for MG treatment. Although it is reasonable to assume that thymectomy can be performed in patients with antibody-positive GMG, the surgery outcome for elder patients with MG, ocular muscle type, and antibody-negative but anti-MuSK-positive patients is still unknown.

Meyer *et al*. compared 48 cases of video-assisted thoracoscopic surgery (VATS) traditional thymectomy and 47 cases of expanded thymectomy, which indicated that there was no difference in the complete cure rate, drug cure rate, and minimum improvement between the two groups after an average of 6-year follow-up visit.[14] Therefore, it can be concluded that the long-term clinical efficacy of the thymus in the minimally invasive treatment and the extended treatment for MG is similar. However, Zielinski *et al*. claimed that the enlarged resection removed more ectopic thymus in the neck and mediastinum after comparisons of 60 cases of transthoracic thymectomy and 58 cases of sternal enlarged thoracic resection after a 6-year follow-up study. It was therefore indicated that the long-term efficacy of expanded resection was more efficient than the classic resection for MG treatment. In this study, we monitored the efficacy of the two therapies of MG for up to 15 months, and the results indicated a significant better recovery and faster recovery rate for patients who received both drug and thymectomy, which were in accordance with a previous research mentioned above.

In a correlation analysis of thymectomy for patients with MG in 2008, Sonett and Jaretzki pointed out that the thymus was present not only in the thymic capsule but also in the adipose tissue around the thymus, which is called the ectopic thymus.[15] However, the study also suggested that it was difficult to find a surgery which can balance the range of resection, complications after surgery, and facilitate the patients' acceptance.

Skeie *et al*.[13] believed that the improvement of the postoperative efficacy of patients with MG can take months or years, and therefore it was difficult to distinguish whether the improvement was due to the effect of thymectomy or immunosuppressive drugs. For our research, the outcome of combined use of thymectomy and bromopyridinium for early-onset MG patients was higher than those who were treated with bromopyridinium alone, suggesting that patients who are insensitive to the therapeutic effects of bromopyridinium can be treated with thymectomy directly.

After adjustments for multiple factors with multivariate logistics analysis, such as age, gender, and severity, previous studies have showed that there was no direct association between the choice for thymectomy and the follow-up efficacy for patients with MG. Patients subjected to thymectomy were more likely to receive aggressive treatments and may get better follow-up efficacy than nonsurgical patients.[5] However, in this study, due to difference in patients' physiological conditions, the improvements of MG benefited from thymectomy may vary between the drug care only and surgical combined with drug therapy groups, and it should be treated more cautiously when considering thymectomy as an effective therapy in patients with tumor-free MG.

In conclusion, this study showed that thymectomy combined with drug therapy could be regarded as one of the options for increasing the probability to cure and as a relief for Nonthymomatous (without Chest Tumor) Myasthenia Gravis (NTMG) patients in China. However, there still exist limitations for this study. For example, a long-term follow-up study, up to years, should also be considered.

Financial support and sponsorship

This work was supported by grant from Shanghai Municipal Health and Family Planning Commission (201540044).

Conflicts of interest

There are no conflicts of interest.

Ji Chen#, Zhiming Chen#, Feng Miao, Yang Song, Gang Chen, Yongjun Zhu, Liewen Pang, Jianying Xi[1], Chongbo Zhao, Xiaofeng Chen

Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai, [1]Department of Neurology, Huashan Hospital, Shanghai Medical College, Fudan University, China

#The first two authors contributed equally to this work

Address for correspondence: Prof. Xiaofeng Chen, Department of Thoracic Surgery, Huashan Hospital, Fudan University, Shanghai, China.
E-mail: xfchen3166@163.com

References

1. Wang W, Chen YP, Wang ZK, Wei DN, Yin L. A cohort study on myasthenia gravis patients in China. Neurol Sci 2013;34:1759-64.
2. Gilhus NE, Verschuuren JJ. Myasthenia gravis: Subgroup classification and therapeutic strategies. Lancet Neurol 2015;14:1023-36.
3. Jaretzki A, 3rd, Barohn RJ, Ernstoff RM, Kaminski HJ, Keesey JC, Penn AS, *et al*. Myasthenia gravis: Recommendations for clinical research standards. Task Force of the Medical Scientific Advisory Board of the Myasthenia Gravis Foundation of America. Ann Thorac Surg 2000;70:327-34.
4. Evoli A. Myasthenia gravis: new developments in research and treatment. Curr Opin Neurol 2017;30:464-70.
5. 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.
6. Gronseth GS, Barohn RJ. Thymectomy for myasthenia gravis. Curr Treat Options Neurol 2002;4:203-9.
7. O'Riordan JI, Miller DH, Mottershead JP, Pattison C, Hirsch NP, Howard RS. Thymectomy: Its role in the management of myasthenia gravis. Eur J Neurol 1998;5:203-9.
8. Romi F, Gilhus NE, Varhaug JE, Myking A, Aarli JA. Thymectomy in nonthymoma early-onset myasthenia gravis in correlation with disease severity and muscle autoantibodies. Eur Neurol 2003;49:210-7.
9. Takanami I, Abiko T, Koizumi S. Therapeutic outcomes in thymectomied patients with myasthenia gravis. Ann Thorac Cardiovasc Surg 2009;15:373-7.
10. Bachmann K, Burkhardt D, Schreiter I, Kaifi J, Schurr P, Busch C, *et al*. Thymectomy is more effective than conservative treatment

for myasthenia gravis regarding outcome and clinical improvement. Surgery 2009;145:392-8.
11. Lisak RP, Levinson AI, Zweiman B, Kornstein MJ. Antibodies to acetylcholine receptor and tetanus toxoid: *In vitro* synthesis by thymic lymphocytes. J Immunol 1986;137:1221-5.
12. Willcox HN, Newsom-Davis J, Calder LR. Greatly increased autoantibody production in myasthenia gravis by thymocyte suspensions prepared with proteolytic enzymes. Clin Exp Immunol 1983;54:378-86.
13. Skeie GO, Apostolski S, Evoli A, Gilhus NE, Illa I, Harms L, *et al*. Guidelines for treatment of autoimmune neuromuscular transmission disorders. Eur J Neurol 2010;17:893-902.
14. Meyer DM, Herbert MA, Sobhani NC, Tavakolian P, Duncan A, Bruns M, *et al*. Comparative clinical outcomes of thymectomy for myasthenia gravis performed by extended transsternal and minimally invasive approaches. Ann Thorac Surg 2009;87:385-90; discussion 390-81.
15. Sonett JR, Jaretzki A, 3rd. Thymectomy for nonthymomatous myasthenia gravis: A critical analysis. Ann N Y Acad Sci 2008;1132:315-28.

DOI: 10.4103/aian.AIAN_138_19

Supplementary Table 1: Patient characteristics in two groups

Feature	Group SM	Group M	*P*
n	25	29	
Age (yr)	42.68±16.36	46.69±16.48	0.3751
Male(%)	38	20	0.15
Primary symptoms			0.857
Blepharoptosis (*n*)	5	3	
general fatigue (*n*)	16	15	
Dysphagia (*n*)	8	7	
course at first diagnosis	21.92±36.19	24.38±36	0.804
osserman at first diagnosis			0.790
IIA	10	8	
IIB	10	14	
IIIA	4	5	
IIIB	1	2	
MGFA at first diagnosis			0.951
IIA	13	14	
IIB	11	14	
IV	1	1	

Supplementary Table 2: MGFA-QMG score between two groups

Time	Group SM	Group M	*P*1	*P*2
at diagnosis	11.04±4.18	13.48±4.87	0.053	
3 month	7.88±3.27	11.52±5.82	0.031	0.262
6 month	5.4±2.96	8.69±5.48	0.027	0.427
9 month	4±2.45	8.21±5.28	0.002	0.0989
12 month	2.8±2.22	6.76±4.43	<0.001	0.156
15 month	2.28±1.81	6.17±4.3	<0.001	0.174

Note: *P*1 indicates the *P* value between two groups in different time. *P*2 indicates the *P* value of the difference in two groups

Supplementary Table 3: MMT- Cranial nerves score between two groups

Time	Group SM	Group M	*P*1	*P*2
At diagnosis	8.32±4.17	9.45±5.08	0.3815	
3 month	5.32±3.50	6.69±5.35	0.2789	0.0017
6 month	2.36±2.12	4.28±4.38	0.0516	4.2907E-10
9 month	1.32±1.25	3.69±3.95	0.0058	5.9924E-13
12 month	0.52±0.87	2.41±2.88	0.0027	8.8212E-18
15 month	0.32±0.56	1.90±2.77	0.0073	2.5036E-19

Note: *P*1 indicates the *P* value between two groups in different time. *P*2 indicates the *P* value of the difference in two groups

Supplementary Table 4: MMT- organism score between two groups

Time	Group SM	Group M	*P*1	*P*2
At diagnosis	10.28±6.69	12.69±11.94	0.38	
3 month	5.12±4.96	9.14±9.88	0.0713	0.0153
6 month	3.44±4.27	6.48±9.03	0.1295	1.7559E-04
9 month	1.92±2.31	5.86±7.88	0.0195	6.5461E-06
12 month	1.40±2.29	4.83±7.33	0.0292	5.0210E-07
15 month	0.56±0.71	3.03±5.14	0.0207	1.0290E-09

Note: *P*1 indicates the *P* value between two groups in different time. *P*2 indicates the *P* value of the difference in two groups

Supplementary Table 5: Total MMT score between two groups

Time	Group SM	Group M	*P*1	*P*2
At diagnosis	18.6±8.48	22.14±14.0	0.2760	
3 month	10.44±6.16	15.83±13.01	0.0638	0.0013
6 month	5.8±4.71	10.76±12.36	0.0644	8.4520E-08
9 month	3.24±2.59	9.55±10.49	0.0050	2.1245E-10
12 month	1.92±2.58	7.24±9.18	0.0071	3.6811E-13
15 month	0.88±0.93	4.9±6.44	0.0030	6.8573E-17

Note: *P*1 indicates the *P* value between two groups in different time. *P*2 indicates the *P* value of the difference in two groups

Supplementary Table 6: ADL score between two groups

Time	Group SM	Group M	*P*1	*P*2
At diagnosis	6.56±2.92	6.72±2.91	0.732	
3 month	4.04±3.43	4.93±3.32	0.209	0.821
6 month	2±1.85	2.9±2.92	0.525	0.384
9 month	1.4±1.89	2.76±2.69	0.025	0.153
12 month	1.44±1.08	2.59±2.73	0.3	0.24
15 month	0.56±0.87	2.31±3.15	0.046	0.058

Note: *P*1 indicates the *P* value between two groups in different time. *P*2 indicates the *P* value of the difference in two groups

Supplementary Table 7: MG-QOL-15 score between two groups

Time	Group SM	Group M	*P*1	*P*2
At diagnosis	22.04±8.65	25.41±14.45	0.357	
3 month	13.2±6.16	20.93±14.31	0.056	0.087
6 month	7.92±4.77	16±12.93	0.059	0.066
9 month	5.28±4.35	13.9±12.08	0.005	0.041
12 month	3.92±4.19	12.17±12.36	0.004	0.057
15 month	2.00±1.87	11.1±11.14	<0.001	0.025

Note: *P*1 indicates the *P* value between two groups in different time. *P*2 indicates the *P* value of the difference in two groups

Supplementary Table 8: Patient characteristics at the end of follow-up

Feature	Chi-square test			Univariate Logistics analysis		Multivariate logistics analysis	
	Group SM (*n*,%)	Group M *n* (%)	*P*	OR (95CI%)	*P*	OR (95CI%)	*P*
Course development (Yes)	4 (16.0%)	14 (48.3%)	0.012	0.204 (0.056,0.744)	0.016	0.534 (0.103, 2.755)	0.453
Crisis (yes)	1 (4.0%)	4 (13.8%)	0.216	0.260 (0.027, 2.500)	0.244	1.886 (0.069, 51.507)	0.707
Deterioration By osserman	0 (0.0%)	4 (13.8%)	0.021	-		-	
Same By osserman	3 (12.0%)	9 (31.0%)		-		-	
Better By osserman	22 (88.0%)	16 (55.2%)		5.958 (1.453, 24.427)	0.013	4.198 (0.793, 22.229)	0.092
Deterioration By MGFA	0 (0.0%)	3 (10.3%)	0.031	-		-	
Same By MGFA	2 (8.0%)	8 (27.6%)		-		-	
Better By MGFA	23 (92.0%)	18 (62.1%)		7.028 (1.380, 35.797)	0.019	6.984 (1.076, 45.337)	0.042