

Could preoperative medication in myasthenia gravis be a cause of the complications following transsternal thymectomy?

Myasthenia Gravis'te ameliyat öncesi medikasyon, transsternal timektomi sonrası komplikasyonların nedeni olabilir mi?

Alper Toker,¹ Türkan Tansel,² Ufuk Alpogut,² Serhan Tanju,¹ Şükrü Dilege,¹
Enver Dayioğlu,² Ertan Onursal²

Departments of ¹General Thoracic Surgery and ²Cardiovascular Surgery,
İstanbul Medicine Faculty of İstanbul University, İstanbul

Background: Complications after transsternal thymectomy for myasthenia gravis were considered to be a major problem. This study was designed to assess the relation between preoperative medication and complications.

Methods: The study group consists of 229 myasthenia gravis patients without thymoma, (164 females, 65 males; mean age 35.6 years; range 9 to 70 years). Postoperative complications and relations with age, gender, duration of symptoms, the clinical stage of the disease, the type of the operative procedure and medication were analyzed. The study population was divided into five groups according to their preoperative medication. Group 1 (n=51) Cholinesterase inhibitors, group 2 (n=30) Corticosteroids, group 3 (n=125) Cholinesterase inhibitors and Corticosteroids, group 4 (n=13) Immunosuppressants, Cholinesterase inhibitors and Corticosteroids, and group 5 (n=10) No medication. Postoperative complications were: *i*) Infectious complications (n=18), *ii*) Myasthenic complications (n=14), and *iii*) Others (n=7).

Results: There was not any statistically significant relation between complications and analyzed data other than subgroup of medications. Patients who had cholinesterase inhibitors, immunosuppressive therapy with additional corticosteroids had increased number of complications (p=0.004).

Conclusion: Concomitant administration of immunosuppressants, cholinesterase inhibitors and corticosteroids to patients with Myasthenia Gravis could increase the number of complications following transsternal thymectomy.

Key words: Myasthenia Gravis/surgery; thymectomy/methods.

Amaç: Myasthenia Gravis hastalığında transsternal timektomi sonrası komplikasyonlar halen önemli bir sorundur. Bu çalışmada, ameliyat öncesi medikasyonla komplikasyonlar arasındaki ilişkiyi ortaya koymak amaçlandı.

Çalışma planı: Transsternal timektomi yapılan ve timomasi olmayan 229 Myasthenia Gravis hastası (164 kadın 65 erkek; ort. yaş 35.6; dağılım 9-70) çalışma grubunu oluşturdu. Ameliyat sonrası komplikasyonlar ile yaş, cinsiyet, semptomların süresi, hastalığın klinik evresi, cerrahi prosedür ve ameliyat öncesi medikasyon arasında ilişki araştırıldı. Çalışma grubu ameliyat öncesi medikasyonuna göre beş gruba ayrıldı: Grup 1 (n=51) kolinesteraz inhibitörleri, grup 2 (n=30) kortikosteroidler, grup 3 (n=125) kolinesteraz inhibitörleri ve kortikosteroidler, grup 4 (n=13) immünsüpressifler, kolinesteraz inhibitörleri ve kortikosteroidler, grup 5 (n=10) medikasyon verilmeyen. Ameliyat sonrası komplikasyonlar ise *i*) enfeksiyon (n=18), *ii*) miyastenik komplikasyonlar (n=14) ve *iii*) diğer komplikasyonlar olarak tanımlandı (n=7).

Bulgular: Komplikasyonlar ile analiz edilen diğer değişkenler arasında tedavi altgrupları dışında anlamlı bir ilişki bulunamadı. Kolinesteraz inhibitörleriyle birlikte immünsüpressif tedavi ve kortikosteroid kullanımıyla komplikasyon gelişimi arasında istatistiksel olarak anlamlı ilişki saptandı (p=0.004).

Sonuç: Bulgularımız, Myasthenia Gravis hastalığında transsternal timektomi uygulanan hastalarda, kolinesteraz inhibitörüyle birlikte kortikosteroid ve immünsüpressif tedavi kullananlarda komplikasyon oranının artabileceğini göstermektedir.

Anahtar sözcükler: Myasthenia Gravis/cerrahi; timektomi/yöntem.

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Correspondence: Dr. Alper Toker. İstanbul Üniversitesi İstanbul Tıp Fakültesi Göğüs Cerrahisi Anabilim Dalı, 34270 Çapa, İstanbul.
Tel: 0212 - 414 20 00 e-mail: aetoker@superonline.com

Currently, treatment for Myasthenia Gravis (MG) consists of cholinesterase inhibitors, corticosteroids, immunosuppressive drugs, short term immunotherapies including plasmapheresis - intravenous immunotherapies and thymectomy. Steroids are the most commonly used and most consistently effective immunosuppressive agents for the treatment MG. They also have the largest array of potential side effects.^[1] Corticosteroids are also known to cause depressive effects on immune system.^[2] Cholinesterase inhibitor agents continue to be used as the first line treatment. Where medical follow up and compliance of the patient with therapy are essential, azothioprine and cyclosporine are the most commonly used immunosuppressants are.

There is a consensus that all adults with generalized MG should have a thymectomy because of the propagated evidence of the safety of the procedure and excellent outcome. The goal of thymectomy is to induce remission, or improvement, permitting a reduction in immunosuppressive medication.^[1] This study specifically focused on postoperative complications and the patients' medication on MG patients.

PATIENTS AND METHODS

We performed 310 thymectomies in myasthenic patients in the past 22 (January 1980-2002) years; the study group comprised 229 patients without a thymoma (164 females, 65 males; mean age 35.6 years; range 9 to 70 years). The indications for thymectomy included myasthenia gravis that compromised the life style, progression of symptoms despite conservative therapy and suspicion of thymoma.

Patients were analyzed according to age, gender, duration of symptoms, clinical stage of the disease, perioperative medication and postoperative complications. Patients were divided into five groups according to their perioperative medication. Group 1 (n=51) Cholinesterase inhibitors, group 2 (n=30) Corticosteroids, group 3 (n=125) Cholinesterase inhibitors and Corticosteroids, group 4 (n=13) Immunosuppressants, Cholinesterase inhibitors and Corticosteroids, and group 5 (n=10) No medication. Patients with no medication were the ones who were considered to be in remission period after a period of medical therapy. Duration of corticosteroid therapy was analyzed postoperative complications were; *i*) infectious complications (n=18): wound infection, sternal dehiscence, sternal osteomyelitis, sternal mobility, mediastinitis, pneumonia, *ii*) myasthenic complications (n=14): reintubation, prolonged intubation, *iii*) others (n=7): gastrointestinal bleeding, atelectasis, pleural effusion, arrhythmia, recurrent laryngeal nerve and transient - persistent phrenic nerve injury. Prolonged intu-

bation was considered a mechanical ventilation period longer than 24 hours.

The thymectomy patients were usually scheduled as the first case of the day and medication was the usual first daily dose of the prescribed drugs. During complete thymectomy with partial sternotomy, all thymic tissue with particular care to neck, aortapulmonary window, and inferior to left innominate vein area was removed with available fat tissues in the mediastinum. Extended thymectomy was employed according to technique described by Mulder.^[3] All patients were given prophylactic antibiotic in the beginning of operation and followed for 3 consecutive days. Neurologists had daily visits after the operation and regimen was managed. In some patients receiving corticosteroids, we employed Robicsek technique^[4] in sternum closure when the sternum was considered to be osteoporotic.

Fisher's exact test and Chi-square test were used for the statistical analyses.

RESULTS

Two hundred and twenty-nine patients were operated, due to MG without a thymoma. Female/male ratio was 2,52. The mean time from diagnosis to operation was 1.9 years (3 months to 6 years). Modified Osserman Genkins classification^[5] of the patients was as follows: Stage 1: 15 patients (6.5%), stage 2: 99 patients (43.2%), stage 3: 81 patients (35.3%), stage 4: 43 patients (14.7%). The employed surgical procedures were complete thymectomy with partial sternotomy in 207 patients (90.3%) and extended thymectomy with complete sternotomy in 22 patients (9.6%). Among all the operated patients, fifty-one (22.2%) were on cholinesterase inhibitor medication, 30 patients (13.1%) on corticosteroid medication only, 125 patients (54.3%) were on corticosteroids and cholinesterase inhibitor medication, 13 patients (5.6%) were treated with cholinesterase inhibitors, corticosteroids and immunosuppressive medication, and 10 patients (4.3%) were given no medication at all. One hundred forty nine patients (65.0%) were extubated in the operating room, 69 patients (30.1%) in the first 24 hours and in 11 patients (4.8%) extubation was delayed from 24 hours to 91 days. Postoperative complications (n=39; 17.0%) were as follows: Pneumonia 7 (3%) patients, mediastinitis 3 (1.3%) patients, wound infection 4 (1.7%) patients, sternal dehiscence 2 (0.08%) patients, sternal mobility 2 (0.08%) patients, gastrointestinal hemorrhage 1 (0.04%) patient, atelectasis 2 (0.08%) patients, arrhythmia 1 (0.04%) patient, pleural effusion 1 (0.04%) patient, reintubation due to myasthenic-cholinergic crisis 3 (1.3%) patients and prolonged intubation 11

(4.8%) patients. Mortality occurred in one patient (%0.4) due to mediastinitis related sepsis.

Other factors. Complications were analysed according to age (over 35 years vs. younger) and gender. Both of them were statistically insignificant factors for the development of complications (Fisher's exact test: $p=0.67$, $p=0.79$). Duration of symptoms, the clinical stage of the disease and the type of the operative procedure (complete thymectomy vs extended thymectomy) were noticed to be statistically insignificant factors ($p=0.42$ and $p=0.48$ and $p=0.07$). In corticosteroid administered patients, duration of corticosteroid therapy (0-6 months vs. 6-12 months vs. more than 12 months) was determined to be a statistically insignificant factor in the development of complications ($p=0.36$).

Medication and complications. The perioperative medication and complications can be seen in Table 1. The incidence of complications was similar between patients receiving corticosteroids with any combination of drugs and patients who were not receiving corticosteroids ($p=0.69$). Patients who were receiving cholinesterase inhibitors and additional immunosuppressant (azathioprine or cyclosporine) therapy with corticosteroids had increased number of complications ($p=0.004$) (Table 1).

Treatment of complications. Infectious complications were treated with conventional therapies. The major complication was mediastinitis. Three patients experienced this complication and one mortality occurred. In all of them our treatment consisted of revision with debridement with appropriate placement of irrigation and drainage catheters and culture specific antibiotics. Myasthenic medication was revised and in two successfully treated patients intravenous immunoglobulin therapy was employed. In sternal dehiscence major consideration was to revise the sternum closure with Robicsek technique with appropriate drainage catheters. Sternal mobility was not treated surgically, preferred approach

was elastic sternal jackets. Plasmapheresis was the most commonly employed procedure in patients with prolonged intubation (7/11 patients, 63%).

DISCUSSION

The patients under evaluation were myasthenia gravis patients without a thymoma. The study was in nonthymomatous patients because we wanted to exclude technical complications due to invasion of thymoma. Preoperative data like age, gender, duration of symptoms, the clinical stage of the disease and type of the procedure were evaluated as statistically insignificant factors for the development of complications. The factor related with postoperative complications was noticed to be preoperative medication. This study demonstrated a higher incidence of complications in patients who were administered immunosuppressive therapy, corticosteroids and cholinesterase inhibitors.

Perioperative medication during the thymectomy procedure in MG is still debatable. Every tertiary clinic developed their own approach for surgical techniques and perioperative medication. No agreement exists on the optimal regimen in the perioperative period of thymectomy for MG. Although some authors prefer immunosuppressants, the majority are in favor of using cholinesterase inhibitors and plasmapheresis in the fear of serious postoperative complications. Seggia and colleagues^[5] demonstrated that, perioperative plasmapheresis improved respiratory function and muscle strength and decreased hospital stay and cost. Our clinic's attitude towards preoperative plasmapheresis is restricted only to severe MG patients who are unable to eat and drink and with restricted pulmonary functions. In the preoperative period only 3 patients (1.3%) necessitated plasmapheresis, whereas 7 (3.0%) of 11 prolonged intubation patients had plasmapheresis in the postoperative period. Plasmapheresis may be used on an urgent basis in myasthenic crisis with respiratory embarrassment. Plasmapheresis and intravenous immunoglobulin therapy have been used widely in the

Table 1. Perioperative medication and number of complications

Medication	Number of patients	Infectious complications	Myasthenic complications	Other complications	Total		
					n	%	p
Chei	51	0	7	2	9	17.6	
Cs	30	4	0	1	5	13.1	
Chei-Cs	125	10	6	2	18	14.4	
Cs-Chei - Isp	13	4	1	2	7	53.8*	($p=0.004$)
No of medication	10	0	0	0	0	-	

Chei: Cholinesterase inhibitors; Cs: Corticosteroids; Isp: Immunosuppressive therapy; Comp: Complications. Patients having any combination of drugs had statistically same ratio of complications Patients who were receiving cholinesterase inhibitors and additional immunosuppressant (azathioprin-cyclosporine) therapy with corticosteroids had increased number of complications ($p=0.004$). Specific type of complications were not statistically significant.

treatment of MG to affect rapid short term improvement.^[6] In some patients with higher stage Osserman-Genkins classification, severe exacerbations and impending crisis combining these two therapies may be advisable, however we are against routine use of these therapies in the preoperative period due to high cost, need for specialized staff and equipment. Our results with higher postoperative complication rates in patients with extended preoperative treatment (cholinesterase inhibitors, immunosuppressants and corticosteroids) suggest that plasmapheresis and intravenous immunoglobulin therapies could be considered for this group of patients in the preoperative period. The evident data would force us to perform the short term immunotherapies in the preoperative period. It is evident from the patients and methods of this article, that corticosteroid therapy was the main medication in the perioperative period. Types of infection (Pneumonia, mediastinitis, wound infection, etc.) which is supposed to be major complication, especially in patients with corticosteroid therapy could not be shown to be an important complication in our study group. In a similar study, postoperative wound infection and mediastinitis were found to be unrelated with the preoperative immunosuppression.^[7] This result supports our data. In another series, the number of postoperative major complications were so high that it is deemed to be unacceptable (71/324).^[8] In this study, postoperative management was administered according to a standardized protocol of anticholinesterase medication, which was withdrawn for the 48 hours of obligatory postoperative mechanical ventilation.^[8] Thus; it is reasonable to continue with the same medication on which the patient has appeared to be in his best condition, even the regimen consists of corticosteroids. Our results demonstrated that our complication rate is 17.0% with such a wide spectrum of defined complications unforeseen in any prior study. Patients having corticosteroids did not have more complications than other patients. But on the other hand; immunosuppressants (azothioprine and cyclosporine) affected the number of postoperative complications adversely. The problem is thought to be due to the operations being transsternal. Probably this combination would cause no complication in minor thymectomy procedures such as video assisted and transcervical. Authors employing these procedures did not offer to taper the regimen in the perioperative period.^[9,10] It was concluded that the long term clinical outcome after transcervical thymectomy is the same as after more radical operations, and also this technique was reported to carry a lower morbidity, a briefer hospitalisation period and a faster recovery.^[11-13] In a study, performed by the author of this article, we found that videothoroscopic thymectomy patients had shorter

duration of chest tube drainage, lesser amount of drainage, shorter hospital stay and lesser visual analogue scale score.^[14]

But even in this less radical approach, immunosuppressive medications (including corticosteroids) were not started until after operation.^[12] We proposed that only addition of immunosuppressants like azothioprine and cyclosporine could cause increase in postoperative morbidity after transsternal procedures. Thus we chose not to start this medication in patients who are candidates of transsternal thymectomy. Corticosteroids were excluded from other immunosuppressants as far as complications are concerned. The other important issue is closure of sternotomy in osteoporotic patients. This problem could be solved by the use of modified Robicsek technique^[4] in closure of sternums after complete and partial sternotomy when the sternum is osteoporotic due to prolonged corticosteroid therapy.

In an extended thymectomy series published recently^[15] the team work of neurologist, thoracic surgeon and anaesthetist was emphasized to improve outcome and to decrease postoperative complications. In this study, the length of hospital stay and the rate of prolonged intubation was reported to be decreased after 1992. Pharmacological control of myasthenic symptoms and the presence of team work in the perioperative setting reduced the incidence of complications. We are supporting this study with fullheart. No complications were encountered including prolonged intubation in the last 25 patients, with an average of 5.6 days of hospital stay after transsternal procedures. It is believed that the approach to MG patients in perioperative period of thymectomy is getting better with the team's cooperation and increasing experience.

In conclusion; in this large series comprising more than two decades, we showed statistically significant relation between postoperative complications and subgroup of medications in patients who had thymectomy for myasthenia gravis. Patients who had cholinesterase inhibitors, immunosuppressive therapy with additional corticosteroids had increased number of complications. Thus we strongly advice to take additional precautions in this subset of patients to prevent complications after thymectomy for myasthenia gravis.

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