Accepted manuscripts are the articles in press that have been peer reviewed and accepted for publication by the Editorial Board of the Vojnosanitetski Pregled. They have not yet been copy edited and/or formatted in the publication house style, and the text could still be changed before final publication.

Although accepted manuscripts do not yet have all bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: article title, the author(s), publication (year), the DOI.

Please cite this article THE NEUROLOGICAL OUTCOME OF PATIENTS WITH MYASTHENIA GRAVIS UNDERWENT THYMECTOMY VIA STERNOTOMY AND VIDEO ASSISTED THORACOSCOPIC SURGERY (VATS)

NEUROLOŠKI ISHOD PACIJENATA SA MIASTENIJOM GRAVIS KOJI SU TIMEKTOMISANI STERNOTOMIJOM I VIDEO ASISTIRANOM TORAKOSKOPSKOM HIRURGIJOM (VATS)

Authors Vesna Martić1, Nebojša Marić2, Vlado Cvijanovic 2, Vojnosanitetski pregled (2019); Online First November, 2019.

UDC:

DOI: https://doi.org/10.2298/VSP190715133M

When the final article is assigned to volumes/issues of the Journal, the Article in Press version will be removed and the final version appear in the associated published volumes/issues of the Journal. The date the article was made available online first will be carried over.
THE NEUROLOGICAL OUTCOME OF PATIENTS WITH MYASTHENIA GRAVIS UNDERWENT THYMECTOMY VIA STERNOTOMY AND VIDEO ASSISTED THORACOSCOPIC SURGERY (VATS)

NEUROLOŠKI ISHOD PACIJENATA SA MIASTENIJOM GRAVIS KOJI SU TIMEKTOMISANI STERNOTOMIJOM I VIDEO ASISTIRANOM TORAKOSKOPSKOM HIRURGIJOM (VATS)

Vesna Martić, Nebojša Marić, Vlado Cvijanovic

1 Clinic for neurology Military Medical Academy, Belgrade, Serbia
2 Clinic for thoracic surgery Military Medical Academy, Belgrade, Serbia

Correspondence to: vesnamartic.bgd@gmail.com
Abstract

Aim. Thymectomy is accepted in surgical treatment of patients with myasthenia gravis (MG). Earlier thymectomy via sternotomy replaces video-assisted thoracoscopic surgery (VATS) as less invasive, last years. The aim of this study was by comparing the neurological outcome to make a conclusion regarding effectiveness and reliability of the two methods of surgical removal of the thymus in patients with MG.

Material and methods. The study included 60 patients with MG who are underwent thymectomy at the beginning their treatment: 30 patients underwent thymectomy via sternotomy, and remaining 30 patients via VATS. In order to evaluate the effect of these two operation techniques we compared data related directly to the operation - the number of post-operative hospital days, the incidence of post-operative complications, as well as data related to the neurological monitoring of these patients: directly after the operation, after one year of surgery and up to three years after surgery.

Results. Data related to the immediate postoperative period indicate significant shorter hospitalisation after the VATS thymectomy ($p < 0.001$), but percentage of postoperative complications in both groups was the same ($p = 0.381$). Clinical deterioration in the first year after operation showed a uniform distribution regardless of the type of performed operation ($p = 0.470$). Number of re-thymectomy in the group underwent thymectomy via sternotomy or via VATS is a borderline statistically significant ($p= 0.054$). Complete stable remission, as a criterion that the thymic tissue was removed in its entirety, was observed in about 11% underwent thymectomy. For other patients, clinical remission is maintained with anticholinesterase and immunosuppressive therapy.

Conclusion. The shorter hospitalization time and faster postoperative recovery, with an equal clinical efficacy and aesthetic component favors the VATS thymectomy compared to thymectomy via sternotomy as more acceptable in the surgical treatment of patients with MG.

Key words: myasthenia gravis, thymectomy, sternotomy, video assisted thoracoscopic surgery (VATS), neurological outcome
Apstrakt

Cilj. Timektomija je prihvaćena u hirurškom lečenju pacijenata sa miastenijom gravis (MG). Ranija timektomija putem sternotomije zamenjena je poslednjih godina video asistiranom torakoskopskom hirurgijom (VATH) kao manje invanzivnom. Cilj rada je bio da poredjenjem neurološkog ishoda izvede zaključak koji se odnosi na efikasnost i pouzdanost ove dve metode hirurškog uklanjanja timusa kod pacijenata sa MG.

Materijal i metode. Studija je obuhvatila 60 pacijenata sa MG koji su timektomisani na početku lečenja: 30 pacijenata je timektomisano sternotomijom a preostalih 30 putem VATS. U cilju procene efekata ove dve operativne tehnike poredili smo podatke koji se odnose direktno na operaciju- broj hospitalnih dana posle operacije, incidenciju postoperativnih komplikacija ali i podatke koji se tiču neurološkog praćenja ovih pacijenata: neposredno posle operacije, posle godinu dana od operacije i do 3 godine iza operacije.

Rezultati . Podaci koji se odnose na neposredni postoperativni period ukazuju na signifikantno kraću hospitalizaciju posle VATH timektomije (p < 0,001), mada je procenat postoperativnih komplikacija u obe grube bio isti (p = 0.381). Kliničko pogoršanje prve godine posle operacije pokazuje uniformnu distribuciju nezavisno od načina operacije (p = 0.470). Broj učinjenih re-timektomija u grupi timektomisanih sternotomijom VATH je granično statistički značajan (p= 0.054). Kompletna stabilna remisija, kao potvrda da je timusno tkivo uklonjeno u potpunosti je ostvarena kod oko 11% timektomisanih. Kod ostalih pacijenata klinička remisija je održavana antiholinesteraznom I imunosupresivnom terapijom.

Zaključak. Kraća hospitalizacija i brži postoperativni oporavak sa podjednakim kliničkim učinkom uz estetsku komponentnu favorizuje VATH timektomiju u odnosu n timektomiju putem sternotomije kao prihvatljivijom u hirurškom lečenju obolelih od MG.

Introduction

Myasthenia gravis (MG) is an autoimmune disease characterized by pathological weakness and fatigue of voluntary muscles. Besides conservative treatment, thymectomy takes an important role in the treatment of patients with MG (9). Surgical removal of the thymus
gland in patients with MG is allows stable clinical course, the greater number of clinical remission, and reduce the dose of drug required in the conservative treatment of the disease (1).

It is believed that the thymus is responsible for the initiation of the immunological processes which cause the occurrence of autoantibodies to the acetylcholine receptor (AChR). Although the association with an anti-MG AChR antibodies by first noticed Lindstrom 1976 (9), the benefit of thymectomy in patients suffering from MG is observed much earlier, at the beginning of the last century. So the first thymectomy in patients with MG was done in 1911 by Ferdinand Sauerbruch by transcervical way, after the x-ray recording of the chest, which has seen increased thymic shadow, and after thymectomy recorded clinical recovery (10). Since transcervical thymectomy proved insufficient because the low visibility and was accompanied by a large number of residual thymic tissue which required re-thymectomy, quickly was replaced via sternotomy.

Thymectomy via sternotomy is described for the first time by Dr. Alfred Blalock in the case of 21-year-old patient with MG followed with her clinical remission for 3 years, in 1939.

Some time after that, in 1941, thymectomy was performed in 7 MG patients without thymoma, with clinical postoperative recovery, also. Blalock published his results in the series of 20 patients in 1944 (9).

Thymectomy via sternotomy as the optimal method of surgical treatment maintain long, until 1993 when David Sugarbaker for the first time made video-assisted thoracoscopy (VATS) with laparoscopic approach the thymus from axillary area which is far less invasive and accompanied by less postoperative scars (15).

Since thymectomy via sternotomy approach requires full and open access to the chest cavity, that leaves a big scar (Figure 1.), VATS thymectomy almost entirely takes its place in recent years (Figure 2.).

In our region VATS thymectomy was first performed in 2012. By the end of 2018 year, at the Clinic of Thoracic Surgery Military Medical Academy, 70 VATS thymectomy done using at first three, then two, and now uniporal VATS thymectomy as the standard (2).
This study compared the results of patients with MG underwent thymectomy via sternotomy and video assisted thoracoscopic surgery (VATS).

**Material and methods**

Among 60 patients with clinical, neuropsychological, immunological and pharmacological verified MG treated at the Clinic for Neurology Military Medical Academy from 2000 to 2018, 30 patients made thymectomy via sternotomy and other 30 via VATS.

VATS thymectomy, as newer surgical technique used at our institution since 2012, and after that all of our patients performed thymectomy by VATS. In patients operated via VATS method was used unipolar technique by one-sided access to the right or left side what was decided by a thoracic surgeon with respect to the anatomical localization of the thymus, but it is more secure access to the right because of the relationship with the brachiocephalic vein.

In relation to the way thymectomy we compared following parameters: age, gender, the length of hospitalization, incidence of complications and lethal outcomes immediately after thymectomy, incidence and treatment of postoperative exacerbations, frequency of re-thymectomy, the length of postoperative recovery.

The goal of thymectomy is complete removal of the thymus gland and mediastinal fat tissue which can be a source of ectopic thymic tissue, which is often not available modern diagnostics. As stable and complete remission is criterion that the thymic tissue was completely removed (17) we followed the postoperative outcome immediately after thymectomy, then one year after operation as well as for a period longer than one year (up to 3 years). In doing so, the clinical status of the patients was assessed by Oserman and Genkins-in (12).

In order to evaluate the effect of these two operation techniques we used to compare data related directly to the operation (the number of post-operative hospital days, the incidence of post-operative complications), as well as data related to the neurological monitoring of these patients in the form of postoperative recurrence and re-thymectomies due to residual thymic tissue. Evaluation of clinical disease achieved by comparing the severity of the
disease evaluated by Osserman and Genkins pre and postoperatively: immediate post-operative, after one year of surgery and up to three years behind that.

Complete statistical analysis of data was done with the statistical software package, SPSS Statistics 18.

Most of the variables were presented as frequency of certain categories, while statistical significance of differences was tested with the Chi square test.

In case of continuous data, variables were presented as mean value ± standard deviation (SD), minimal and maximal values. Kolmogorov-Smirnov test was used for evaluation of normal data distribution. According to the results of this test, statistical significance between groups was tested by t-test or alternatively by Mann-Whitney or Wilcoxon test.

All the analyses were estimated at p<0.05 level of statistical significance.

**Results**

As in the total population of our patients (43 women and 17 men), and in both groups operated by different techniques, significantly are dominated women: 70.6% in group with thymectomy via sternotomy and 76.9% in the group operated via VATS (p <0.001); so there were no statistically significant differences in the distribution of the sexes in both groups.

The average age of our patients in the total population was 41.67 ± 13.90 years (min 28, max. 65) and there were no statistically significant differences in age among the sexes (p = 0.236) or between groups of patients operated by different techniques (p = 0.486).

The average duration of hospitalisation for patients operated via sternotomy was 10.13 ± 2.604 days (the shortest 4 and the longest 16 days) while the average duration of hospitalisation for the operated by VATS was 5.04 ± 1.661 (minimum of 2 and maximum of 9 days). Comparing the duration of the hospitalization in relation to the manner thymectomy was performed, statistically significantly longer hospitalization was after thymectomy via sternotomy (p < 0.001).

Among the postoperative complications, all patients have reported soft and transient paresthesia in the operated area who withdrew in the first few postoperative months. Among the more serious complications, there was one death during the first week of
operation due to myocardial infarction in group operated via sternotomy, which proved to be statistically insignificant in terms of post-operative complication among patients operated with different surgical techniques (p = 0.381). Pneumonia and myasthenic crisis, which is often mentioned as a possible post-operative complications, have not been seen among our patients (17).

Clinical condition of our patients evaluated according Osserman and Genkins before starting treatment and thymectomy and after an operation on the day of discharge from the clinic.

With regard to the recommendation that thymectomy should be done when the patient is stable, patients achieved clinical remission with medicaments first, and followed that thymectomy performed.

As the MG is heterogeneous disease, has not accepted a single standard in the treatment of this disease as the best for anyone with MG (14). Pyridostigmine whose initial therapy dose should be adjusted to the symptoms of the disease. Corticosteroids and immunosuppressive therapy are introduced when Pyridostigmine is not enough to achieve therapeutic goals (13, 14).

The average clinical condition in patients before operation via sternotomy was 2.65 ± 0.702 (2 minimum, maximum 4), and after the operation 1.20 ± 1.08 (min 0, max. 3) which indicates a statistically significant recovery (p = 0.002). The average preoperatively clinical condition of patients operated via VATS method was 2.0 ± 0.75 (min 1, max. 4) and after operation 1.0 ± 1.0 (min. 0, max 3), what indicate statistically significant postoperative recovery, also (p≤ 0.001). In addition, there was no significant difference in the preoperative severity MG between the patients treated with different surgical techniques (p = 0.062). Conclude that there is significant clinical improvement after thymectomy via sternotomy and VATS method (p = 0.01). A comparison of the immediate postoperative outcomes, it was concluded that both operational techniques are equally successful when it comes to the immediate post-operative recovery (p = 0.762).

Patients with medication held in a state of clinical remission during postoperative recovery. Under clinical remission considered a situation where the patient is disease-free, wherein they may have some weakness in the closure of the eyes but without any other weakness of the muscle (14).
In the postoperative period, the dosages of corticosteroid was carefully reduced because any reduction of the dose of the drug carries a risk of relapse. Non-steroidal immunosuppressive drugs were added when corticosteroid therapy was not enough or when you want to avoid its adverse effects. Of non-steroidal immunosuppressive drugs, according to the consensus of experts, Azathioprine is in the first place for the treatment of MG which is respected in group of our patients, who are well tolerated and without any side effects from the therapy with Azathioprine (13, 14). The deterioration of their condition is most frequently occurred in the abrupt reduction in therapy, due to an infection or due to residual thymic tissue. Therefore, clinical deterioration was the indication of the control scener of the chest: in 3 of the patients seen rest of thymic tissue, which is an indication for reoperation (Graphic 1.) All 3 reoperated patients were operated via sternotomy previously. Among the reoperated patients, two was made sternotomy again, but one patient are performed VATS. This difference in the number of reoperated patients treated with the diferent techniques, is borderline statistically significant (p = 0.054). There were no complications in reoperated patients.

During the first year after surgery, clinical deterioration was at 24 patient underwent sternotomy (80% of patients) and in the group via VATS deterioration was noted in 15 patients (65.2%). This difference in percent was not statistically significant and there is a homogeneous distribution of deterioration regardless of the type of surgery (p = 0.470).

We have observed recorded patient, reoperated via sternotomy, during the first year after surgery were deterioration provoked by infectious syndrome.

In patients without rest of thymic tissue, clinical deterioration are solved by raising the dose of the existing anticholinesterase and corticosteroid therapy (80% operated via sternotomy and 56.5% via VATS operated), the introduction of azathioprine (Imuran) in the therapy (at 20% operated via sternotomy and 34.8% patients VATS operated), and with therapeutic plasma exchange (PE) (0 in the operated via sternotomy and 8.7% in the group operated via VATS) since the PE useful when other therapies are not sufficient, or when it is necessary to minimize the exacerbations (14). Using HI-square test (p = 0.325), it was concluded that there were no statistically significant differences in the treatment of deterioration of the patients operated by various techniques or that have the same therapeutic principle any deterioration treated.
Reliable data about our patients in the next two years were obtained only for 34 patients: for 12 operated via sternotomy and 22 operated via VATS. In the observation period of 3 years of thymectomy, 2 patients of both operated group were in complete clinical remission - disease symptom-free and without treatment for a period of one year (8).

Second group of patients was only on Mestinon: 3 patients operated via sternotomy and 1 patient operated via VATS included. A third group of patients was on Mestinon and on corticosteroid therapy: 2 patients underwent sternothomy and 6 patients operated by VATS.

Four group was treated with Imuran: 5 patients operated via sternotomy and 13 operated via VATS. None of the patients had PE after a year of thymectomy (Graph. 2).

The Chi-square test showed that the kind of treatment did not significantly different in patients operated by different techniques more than one year after the operation (P = 0.358).

Due to pathohistological (PH) findings in the operated thymus, we distinguish atrophic thymus, hyperplasia thymus and the thymoma. In group operated via sternotomy, 2 patients had atrophic thymus, 1 thymoma and the 27 patients thymic hyperplasia. In VATS group operated, atrophic thymus had 3, 1 had thymoma and 26 patients thymic hyperplasia.

Among our patients one was seronegative; he treated by VATS, and in this patient was seen thymic hyperplasia.

Pathohistological type of thymus was almost uniform in the group of patients operated via sternotomy and thus patients operated via VATS (P = 0.896).

A total of 5 patients was found atrophy of the thymus. The average age of these patients was 67.60 ± 6,986; and it was statistically significant difference as compared to patients with thymic hyperplasia and thymoma (p < 0,001).

**Discussion**

Thymectomy is an option which can minimize or even avoid immunosuppressive therapy in seropositive generalized myasthenia (18). It is suggested in younger than 45 years of
age, with the advice to be done as soon as possible, because then the better the results of treatment (19).

Younger patients with a less severe and shorter duration of the disease, more likely have a complete remission after thymectomy (1).

Thymectomy is done in seronegative generalized MG patients also, when there is weak and uncertain response to immunosuppressive therapy (14).

If the patient does not respond or has insecurely course to immunosuppressive therapy or there is side-effects after its initiation, thymectomy is the method of choice in the elderly patient, also. As we followed this recommendation, the average age of our patients was 41.67±13.902 years.

All MG patients with thymoma should be operated (14).

Women were dominant in our group of operated patients, corresponding data from the literature where a higher incidence of women in the MG early onset (before the age of 50), in which thymectomy and primarily indicated (5).

Publications of sporadic positive effect of thymectomy on the clinical course of patients with MG (15, 7) have been recently replaced by publications which compared the clinical course of patients treated surgically and conservatively.

One of them is shown significantly more likely achieved clinical remission after thymectomy than without the operation (20% vs. 10%) (6).

In our group of a total of 60 patients is noted significant improvement in the clinical picture of patients directly after thymectomy (p = 0.01).

Effect of thymectomy in different decades in the period from 1940. to 2000. was followed by the another large study (6) when observed that in all the decades, number of patients in complete clinical remission is about 10%. It corresponds to our results- about 11% of our patients was in complete clinical remission and without treatment for a period longer than one year (6). The number of patients who had postoperative recover gradually grew from 30% to almost 60% at the closing decade of the year 2000. Clinical remission of our patients was achieved by combining differently anticholinesterase and immunosuppressive drugs but no patient is required PE in the period after one year after thymectomy.
The percentage of subjects (6) which are continued to deteriorate and those who died decreased from decade to decade, what perhaps explain modern concepts of pharmacological treatment of this disease.

It is known that MG with early or late beginning have different HLA gene and various autoimmune targets, but the same mechanism of development. The existence of different targets of autoimmunity confirms differences in thymic pathology: follicular hyperplasia of the thymus is often seen in early onset seropositive MG, whereas atrophy of the thymus is the most common finding in late-onset MG (MG 15-20%) (9). There is an equal distribution of different PH findings of thymus: thymoma, thymic atrophy and hyperplasia (P = 0.896) among our patients operated by diferent techniques.

Atrophic thymus was found in our five patients (16.7%). Their average age was significantly older (67.60 ± 6.97) compared to the age of the patients with hyperplasia and thymoma (p < 0,001), corresponding data from the literature. Thymoma is seen in 10 to 15% of cases (10), usually between 45 and 55 years of age, which corresponds to our results because in one patient in both groups, thymoma was found.

Comparing the effects of thymectomy via sternotomy or via VATS most commonly observed parameter directly related to the operation such as the duration of the operation, intraoperative blood loss, the perception of pain, duration of hospitalization, the need for artificial respiration, post-operative complications resulting in death (16, 3) where it gives a certain advantage to thymectomy via VATS due to shorter hospitalization, a minor loss of blood and to better cosmetic effect. A meta-analysis of 12 studies that dealt with this problem gives also the advantage VATS thymectomy because fewer post-operative complications and and less frequency of myasthenic crisis (17). Similar data were obtained in our group of patients: significantly longer hospitalization after sternothomy (p < 0,001), one death in the group operated via sternothomy which did not come out statistically significant while myasthenic crisis and pneumonia, which is often referred as post-operative complications in the literature, not observed among our patients (17).

The incomplete removal of the thymus leads to an unstable postoperative course while a complete stable remission is criteria that the thymic tissue was removed in its entirety (17).
Therefore, apart results related directly to the operation, we followed our clinical status of patients immediately after surgery, then after one year and 3 years of operations.

Immediate post-operative recovery was statistically significant ($p = 0.002$), and both operational techniques were equally effective ($p = 0.762$).

Number of clinical deterioration in the first year of operation showed that there is a homogeneous distribution of deterioration regardless of the type of surgery ($p = 0.470$). In 3 patients the cause of deterioration was rest of thymic tissue, which is an indication for re-thymectomy.

All 3 patients who have need for re-thymectomy, were previously operated by sternothomy. This difference in the number of re-thymectomy between patients treated by various techniques was statistically significant ($p = 0.054$).

Other exacerbation was solved by correcting anticholinesterase therapy and corticosteroids, introduction azathioprine and series of PE.

It was concluded, that there were no statistically significant differences ($p=0,325$), in the treatment of deterioration in the patients operated by various techniques.

Three years after surgery, two patients in both operated group (around 11%) were in complete clinical remission: symptom-free and without treatment for a period longer than one year (8). Other patients were on combination anticholinesterase therapy and immunosuppressives , and none of them had need for PE. Types of treatment after 3 years of operation is not significantly different in patients operated by a variety of techniques ($P = 0.358$).

**Conclusion**

It can be concluded that the sternothomy and VATS thymectomy achieve equal clinical results, but shorter hospitalisations, and better cosmetic effect favored VATS as it is now more acceptable technique for thymectomy in patients with MG.
Figures

Figure 1 - scar after thymectomy via sternotomy

Figure 2 - scar after thymectomy via VATS

Graphics

Graphic 1. Number of re-thymectomy in the first year of thymectomy
Graphic 2. Clinical outcome and therapy 3 years after surgery (% of patients)

Literature

1. Beghi E, Antozzi C, Batocchi AP, Cornelio F, Cosi V, Evoli A, et al. Prognosis of myasthenia gravis: a multicenter follow-up study of 844 patients. J Neurol Sci. 1991;106(2): 213-20.

2. Caronia FP, Arrigo E, Trovato S, LoMonte Al, Cottone S, Sgalambro F et all.

3. Uniportal bilateral video-assisted sequential thoracoscopic extended thymectomy. J Vis Surg. 2017; 3: 69. doi: 10.21037/jovs.2017.03.29. eCollection 2017. Review

5. Chang PC, Chou SH, Kao EL, Cheng YJ, Chuang HY, Liu CK et al.. Bilateral video-assisted thoracoscopic thymectomy vs exendend transsternal thymectomy in myasthenia gravis: a prospective study. Eur Surg Res 2005; 37(4); 199-203.

6. Lo CM, Lu HI, Hsieh MJ, Lee SS, Chang JP. Thymectomy for myasthenia gravis: Video assisted versus transsternal. J Formos Med Assoc. 2014, 113 (10), 722-6.

7. Fan L, Ma S, Yang Y, Yan Z, Li J, Li Z. Clinical differences of early and late-onset myasthenia gravis in 985 patients. Neurol Res. 2018, 12: 1-7.

8. Grob D, Brunner N, Namba T, Pagala M. Lifetime course of myasthenia gravis. Muscle Nerve 2008; 37: 141-9.

9. Grob D. Course and management of myasthenia gravis. JAMA. 1953; 153 (6): 529-32.
10. Jaretzki A, Barohn RJ, Ernstoff RM, Kaminski HJ, Kesey JC, Penn AS, Sanders DB.. 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 (1): 327-34.
11. Kirschner PA. Alfred Blalock and thymectomy for myasthenia gravis. Ann Thorac Surg. 1987; 43 (3): 348-9.
12. Kirschner PA. The history of surgery of the thymus gland. Chest Surg Clin N Am. 2000; 10 (1): 153-65, Review.
13. Lennon VA, Lindstrom JM, Seybold ME. Experimental autoimmune myasthenia gravis: cellular and humoral immune responses. Ann N Y Acad Sci. 1976; 274: 283-99.
14. Osserman, Genkins G. Studies in myasthenia gravis: review of a twenty-year experience in over 1200 patients. Mt Sinai J Med (NY). 1971: 38 (6): 497-537.
15. Palace J, Newsom-Davis J, Lecky B. A randomized double-blind trial of prednisolone alone or with azathioprine in myasthenia gravis. Myasthenia Gravis Study Group. Neurology. 1998; 50 (6): 1778-83.
16. Sanders DB, Wolfe GI, Benatar M, Evoli A, Gilhus NE, Illa I et all. International consensus guidance for management of myasthenia gravis. Neurology. 2016; 87(4): 419–25.
17. Sugarbaker DJ. Thoracoscopy in the management of anterior mediastinal masses. Ann Thorac Surg. 1993; 56 (3): 653-6.
18. Zahid I, Sharif S, Routledge T, Scarci M. Video-assisted thoracoscopic surgery or transsternal thymectomy in the treatment of myasthenia gravis? Interactive Cardiovas Thorac Surg. 2011, 12 (1), 40–6.
19. Qi K, Wang B, Zhang LB, Chu XY. Video assisted thoracoscopic surgery thymectomy versus open thymectomy in patients with myasthenia gravis: a meta analysis. Acta Chirurg Belg 2016. http://dx.doi.org/10.1080/00015458.2016.1176419
20. Wilkens KB, Bulkley GB. Thymectomy in the integrated management of myasthenia gravis. Adv Surg. 1999; 32:105-33.
21. Sussman J, Farrugia ME, Maddison P, Hill M, Leite MI, Hilton Jones D. Myasthenia gravis: Association of British Neurologist management guidelines. Pract Neurol. 2015; 15(3): 199-206.

Received on July 15, 2019.
Revised on November 25, 2019.
Accepted November 25, 2019.
Online First November, 2019.