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VATS THYMECTOMY AS METHOD OF CHOICE IN SURGICAL TREATMENT OF PATIENTS WITH MYASTHENIA GRAVIS

VATS TIMEKTOMIJA KAO METODA IZBORA U HIRURŠKOM TRETMANU PACIJENATA OBOLELIH OD MIJASTENIJE GRAVIS

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Myasthenia Gravis, Thymectomy, Video-assisted thoracoscopic surgery (VATS), Surgical technique, Benefits, Treatment, Management.

Ključne reči

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Abstract

In the last two decades minimally invasive video assisted thoracospopic surgery (VATS) is increasingly accepted in many medical centers around the world as preferred technique in surgical approach for thymectomy. The most common indication for VATS thymectomy is management of myasthenia gravis (MG). This surgical technique, in regard to transsternal approach (traditional approach), provides results with a minimal access trauma which leads to better preservation of pulmonary function and significantly reduced postoperative pain, shorter hospital stay, incomparably better esthetic results and equivalent outcomes.
The purpose of this article is to point out benefits and technique of VATS thymectomy and so encourage physicians to motivate patients and advocate early surgical management of myasthenia gravis in order to increase probability of remission or improvement.

INTRODUCTION

Myasthenia gravis (MG) is a chronic progressive disease which is characterized by weakness and fatigability of skeletal muscles caused by defects in neuromuscular transmission [1]. In 85% of the cases this is due to the existence of auto-antibodies against acetylcholine receptors (AchR) [2, 3]. As the thymus gland has important role in creation of this AchR auto-antibodies [4], thymectomy interrupts process of autoimmunization and reduce number of circulatory auto–antibodies [5], thus increase probability of remission and improvement.

History

MG has long history of over three centuries. First described case of MG is of the Indian chief Opechankanough who died in 1644 [6]. Ferdinand Sauerbruch performed first thymectomy in 1911 using a transcervical approach [7]. In 1936 Blalock became the first person to perform a transsternal thymectomy because of a thymic tumor. Patient also had severe generalized MG. Postoperative he noticed improvement in myasthenic symptoms [8]. Soon, Blalock and colleagues reported series of myasthenic patients who improved after thymus removal and suggested thymectomy for the management of MG [9]. Since then thymectomy is recognized as valuable tool in MG treatment.

Epidemiology

Epidemiological characteristics of MG in Serbia collected during the period 1983-1992 showed prevalence of about 77 and the average annual incidence of about 3.7 cases per million population. The mortality rate was 0,2 per million population [10].

MG can occur at any age, but it is characterized by two peaks of onset age which are related to sex so we say that non–thymomatosus MG (NTMG) is disease of young females (13 – 30 years of age) and older men (50 – 70 years of age), with a predominance of female in younger age (3:1 to 4:1), and predominance of man in older age (2:1) [11]. In thymoma–associated MG (T-MG) there is no difference between sexes.

Signs and Symptoms of MG

Start of disease is slow and nonspecific and it is usually preceded by an initially disorder such as infections, pregnancy, stress or surgical procedure. Also, disease is characterized by periods of exacerbations and spontaneous remission.

Myasthenia gravis can affect any voluntary muscle (generalized MG) or stay limited only to the extra ocular muscles (ocular MG). Symptoms and signs of disease are related only with motor activity, there is no change in skin sensation, coordination or reflexes

Although every skeletal muscle or muscle bulk can be affected, in 75% of patients MG initially affects extra-ocular muscles (ocular MG) leading to ptosis and/or diplopia. If ocular MG persist for more than three years it is unlikely that it will be generalized, however, in 80% of patients during 1st year and in 85% during 2nd year from onset of the disease illness spreads to other groups of skeletal muscles (generalized MG). Beside extraocular, most commonly affected in this medical condition are facial muscles (lack of facial expression), oropharyngeal muscles (bulbar weakness – tongue weakness, feeding difficulty i.e. weakness in chewing and dysphagia), limb muscles (limb weakness) and axial skeletal muscles (neck weakness, vocal cord paralysis, difficulty in breathing, urinary incontinence).

The most severe symptom and life threatening in MG is respiratory failure (myasthenic crisis) which is caused due severe reversible weakness of inspiratory muscles and/or vocal cord paralysis. Also difficulty in breathing can occur due obsturction by mucus or saliva which can't be eliminated because respiratory muscle weakness disables effective cough. In this condition it is most important to anticipate the need for respiratory assistance rather than deal with emergency intubation [12].

By most common Oserman's clinical classification based on course of disease, general MG can be further subdivided into mild, moderately severe, acute fulminating and late severe form of disease [Table 1] [13].

***Table 1**. Modified Clinical Classification of MG (Osserman and Genkins 1971)*

Type	Adult forms	%*	Characteristics	Response to therapy	Mortality No
I	Ocular MG	15-20%	Involvement restricted to extra – ocular muscles ptosis and/or diplopia	Good	Low
II –A	Mild generalized MG	30%	Generalized weakness without respiratory muscle involvement	Good	Low
II–B	Moderately severe generalized MG	20%	More severe generalized involvement, bulbar symptomscommon and relative sparing ofrespiratory muscles	Satisfactory	Low
III	Acute fulminating disease	11%	Rapid onset (less than 6 months) of respiratory muscle involvement	Low	High
IV	Late severe disease	9%	Severe symptoms that have progressed for more than 2 years after onset of ocular or mild generalized MG	Low	High

* Percent of all MG forms

***Table 2**. Classification of MG by age*

MG	Etiopathogenesis	Onset age	Sex	Thymic gland	Flow
Congenital	autosomal – recessive pattern (hereditation)	0–2	female > men	normal	long survival
Neonatal	passive transfer of autoantibodies from myasthenic mother	Infant	female = men	normal	no more than 6 weeks after birth (transit)
Juvenile	autoimmune	0–20	female > men	hyperplasia	slow progression
Adult	autoimmune	20–40	female > men	hyperplasia	from slow to fast progression
With late age onset	autoimmune	56–60	men > female	thymoma	fast progression

Management of MG

Choices in treatment of MG are **medical** (anticholinesterase, immunosuppressive, plasmapheresis, intravenous immunoglobulin) and **surgical** (thymectomy).

First line of treatment for generalized MG should be *anticholinesterase* medications (increase neuromuscular transmission) and thymectomy. *Thymectomy* and *corticosteroids* (medical thymectomy) have a same goal to lower quantity of antibodies. Corticosteroids should be used, as second choice in treatment of MG, when there is lack of clinical improvement after therapy with acetylcolinesterase inhibitors. Also, they can be used in pre-operative period in preparation for thymectomy but they shouldn't be considered as replacement for surgical treatment.

Myasthenic patients during treatment can experience two types of crisis. *Cholinergic* crisis develop due to excessive dosing of anticholinesterases while *myasthenic crisis* may occur due to insufficient medication. This two crisis can be differentiate by diameter of pupils (miosis at cholinergic and mydriasis at myasthenic crisis) and with use of edrophonium (Tensilon), a short-acting acetylcholinesterase inhibitor, which leads to positive response in myasthenic crisis.

Nowadays in neurology, separation on this to types of crisis is outdated and now it is always about myasthenic crisis.

Plasmapheresis and *intravenous immunoglobulin* (IVIG) are therapies which are used during myasthenic exacerbation to produce short-term clinical improvement by lowering circulating antibodies.

Surgical vs. Medical Management of Myasthenia Gravis

Review article by Gronseth and Barohn which included 21 controlled but nonrandomized studies describing outcome in MG showed positive associations between thymectomy and MG remission or improvement. Patients with nonthymomatosus MG who were treated by surgical approach were 2.1 time as likely to attain medication-free remission, 1.6 time as likely to become asymptomatic and 1.7 time as likely to improve compared to patients who were treated only by medical therapy [15].

Surgical Treatment of Myasthenia Gravis – Thymectomy

As mentioned before thymus has important role in pathogenesis of MG. About 80% of MG patients have abnormal thymus. Current estimates are that about 65% of MG patient have lymphoid follicular hyperplasia, about 15% have thymoma and that about 30% of patients with thymoma have MG [16].

Surgical removal of thymic gland (thymectomy) is safe and effective therapy option for MG [17]. Studys showed that MG patients undergoing thymectomy are more likely to achieve medication-free remission, become asymptomatic, and improve (lower Osserman stage or same stage on fewer medications) than MG patients who aren't treated by thymectomy [15]. Thus, its goal, as a treatment for MG, is to induce remission or at least to enable the dose reduction of immunosuppressive drugs [1].

Thymectomy is indicated for nonthymomatosus generalized autoimmune MG in younger age patients (40 % have improved symptoms and 25% have complete remission) and in all MG patients with thymoma (less effective results in MG remission but there is an oncological purpose – to prevent spread of thymoma) [18, 19].

Benefit of thymectomy in strictly ocular non thymic MG and in elderly patients (late onset MG) remains to be established [20, 21].

Thus, most likely chances to benefit from thymectomy have younger age groups, patients with generalized non thymomatosus MG, and all patients with thymoma [19].

Remission rate depends from number of factors:

1. *Completeness of resection*. The less thymus left behind, the higher the remission rate [22]. Removal of perithymic fat substantially increases probability for complete stable remission (CSR) because anterior mediastinal fat may contain microscopic thymic tissue (up to 98% of patients). If thymectomy doesn't achieve any results probably the main cause is incomplete resection which occurs mostly because of ectopic localization of thymic tissue [23-25].

2. *Severity of MG*. Mild MG patients have better outcome after thymectomy in regard to severe (by Osserman Class 2b, 3 or 4) but severe patients who are treated with thymectomy are 3.7 time as likely to achieve remission than severe who are not surgically treated [15].

3. *Duration of disease.* Early surgery can substantially increase chances to complete stable remission. Patients who were surgically treated soon after illness onset may be twice as likely to achieve remission [26-28]. Best results are achieved when surgery is performed during the first year from onset of illness.

4. *MG onset age*. Patients with early onset age may have better chance to achieve CSR and medical – free remission [26].

5. *Thymic pathology*. Patients with thymoma–associated MG (T-MG) have lover chance for CSR rate than non–thymoma MG (NT-MG) patients. In Study by Magi et al. after thymectomy in 197 T–MG patients 9.64% showed CSR, 44.16% were asymptomatic, 34.52% achieved medical free remission [19].

6. *Time after thymectomy.* Results of thymectomy shouldn't be expected immediately after surgery, remission rate increases as post-operative time goes.

There are several different conventional thymectomy approaches for treatment of MG. The most common is transsternal, while others are transcervical, and combination of transcervical and transsternal thymectomy [table 3.] [29].

Table 3. *Thymectomy Classification of the Myasthenia Gravis Foundation of America*

	Surgical approach	Variation
T1	Transcervical thymectomy	Basic
		Extended
T2	Videoscopic thymectomy	Classic
		Extended
T3	Transsternal Thymectomy	Standard
		Extended
T4	Transcervical and transsternal thymectomy	

Fig. 1. *Chest CT scans – Radiographic manifestations of thymic pathology in MG*

Experience of our team at MMA in preoperative, surgical and postoperative management of MG is extensive. Open surgical technique, i.e. transsternal approach, was used until we introduced VATS thymectomy in 2012. Since then to December 2014, 23 patients were successfully operated using unilateral two or three portal VAT thymectomy.

Left – or right–sided approach was selected in regard to preoperative CT status of the thymus (Fig 1).

If projection of the thymus was on middle line then right-side approach was prefer due to anatomical structures and well demarcation between thymic region and the superior vena cava (Fig. 2).

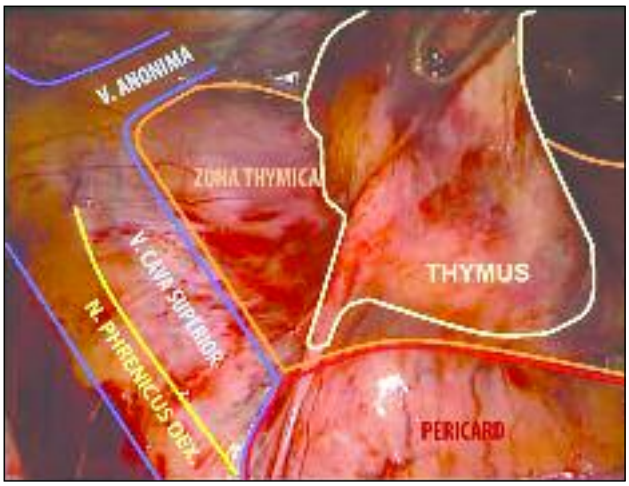

Fig. 2. *Right sided thoracoscopic view on anterior mediastinum with important anatomic landmarks.*

Absolute contraindication for this technique would be extensive adhesion that obliterates the pleural space and prior pleurodesis. Relative contraindication is previous ipsilateral thoracotomy or inability to tolerate single lung ventilation and cardiomegaly for left side approach.

Surgical technique

Surgical team consists of surgeon, surgeon's assistant, anesthesiologist, scrub nurse and circulating nurse. Preoperative contrast – enhanced CT of thorax and spirometry are mandatory. Two units of cross matched blood should be provided. Urinary and central venous catheters are not necessary. During surgical procedure patient is under general anesthesia intubated with double lumen edotracheal tube (Carlens) which provides selective left lung ventilation and collapse of right lung. This is essential because it facilitates access and allows clear view of the mediastinum. The patient is positioned in partial lateral left decubitus position (Fig. 3).

Three small incisions are made through which ports are placed (5mm to 10mm port). Port for scope is usually in fifth intercostal space (ICS) of the level of the anterior or midaxillary line. Instrument ports are usually placed in anterior axillary line for two ICS caudal and cephalad (third and seventh ICS) to the scope port. (Fig. 4).

After insertion of thoracoscope into right pleural cavity and examination of hemithorax, with special attention to the mediastinum and clearly identification of phrenic nerve, procedure begins with incision of the mediastinal pleura anterior to the phrenic nerve at the inferior portion of pul-

Fig. 3. *Patient's position*

Fig. 4. *Port placement's on the right chest wall.*

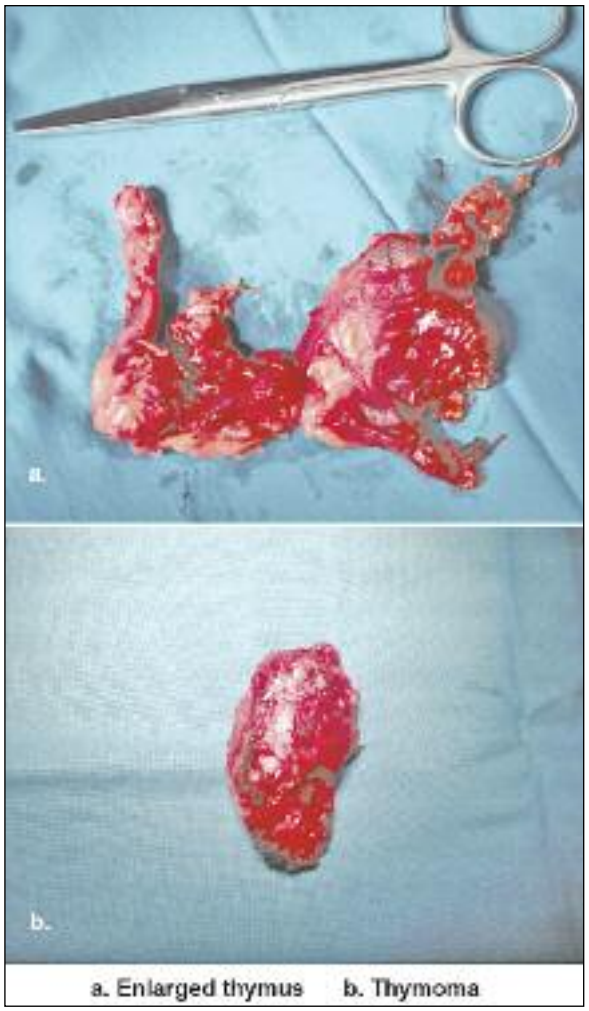

Fig. 5. *Examples of Specimens Obtained by VATS Thymectomy.*

monary hilum and goes caudally and medially to the anterior edge of the phrenic nerve, whose damage must be avoided, to contralateral mediastinal pleura and cardiophrenic space .

Completely pericardial fat (may contain thymic tissue) is separated from pericardium without breaching it.

After careful dissection the superior vena cava – brachiocephalica junction is identified. Further dissection is then carried to the left towards identifying one to three thymic veins, which drains into the left brachiocephalic vein, securing them with two vascular clips and dividing them between clips. After resection, with preserving venous angle and aortic arch, thymus gland is removed en bloc with mediastinal fat through middle port under direct vision. Thymus is then inspected to determine completeness of resection; classic anatomic form should be seen (Fig. 5).

Specimen is submitted for pathology examination. Operative field is checked for haemostasis and aerostasis. Under direct vision one chest tube is placed in pleural space through lower incision (seventh ICS). After that, the lung is reinflated under direct vision. Suture of other two incisions completes the operation. In most cases patients are extubated in operating room [30].

DISCUSSION

As mentioned previously, first cervical approach in treatment of MG was by Sauerbruch in 1911 and first transsternal approach in 1936 by Blalock. Since then there is an ongoing debate about the most suitable surgical approach which was further „complicated" in 1993 by Sugarbaker who described, for the first time, minimally invasive thoracoscopic approach for thymectomy [31].

Conventional surgical approaches are transsternal and transcervical.

Transsternal approach for thymectomy (full for thymic mass e.g. thymoma or partial for MG) provides the excellent surgical exposure of the thymus but it is associated with larger surgical access trauma, increased morbidity, longer hospital stay and longer recovery time in these patients.

Transcervical approach is less prefer due to limited exploration of mediastinum, removal of ectopic thymic tissue and hemorrhage control.

Since 2012 at our institution *VATS* is preferred approach for thymectomy. This approach in regard to traditional transsternal offers equivalent CSR with significantly reduced access trauma which leads to much reduced postoperative pain, morbidity, mortality, blood loss (68ml VATS < transsternal 154.1ml) [32], better preservation of pulmonary function[33], shorter hospital stay, shorter recovery time, lower costs, better quality of life and incomparably better esthetic results (Fig. 6), especially important for young female population which represent the significant majority of patients [25, 28, 32-36].

One more advantage of VATS approach, which is not the case with transsternal, is that mammary artery is preserved. That is especially useful for patients which will in future have a need for bypass cardiac surgery.

On the other hand, main concern about VATS thymectomy is completeness of resection. But studies showed that VATS approach has equivalent remission rate as traditional transternal approach with significantly less morbidity [34-36], which coincides with our preliminarily observation after 23 VATS thymectomy. This is mainly because this technique provides excellent surgical view on anterior mediastinal compartment which allows fully removal of anterior mediastinal fat with the thymus gland.

Because of aggressive surgical approaches majority of patients were unwilling to take surgical treatment for MG, although early surgery is in direct association with remission rate. Now safety and efficiency of this operative technique contributes to significantly earlier and more frequent indication for its performance which leads to more successful treatment of MG patients.

However, it should bear in mind that VATS thymectomy is advanced VATS technique and should be done only by trained surgeons with extensive experience in VATS surgery.

CONCLUSION

MG patients undergoing thymectomy are more likely to achieve medication-free remission, become asymptomatic, and improve than MG patients who aren't treated by thymectomy. VATS thymectomy is safe and effective method for inducing remission or at least for improvement, permitting a reduction in immunosuppressive medication. In regard to traditional sternal splitting operation it offers equivalent remission rate with significantly reduced access trauma which is associated with much reduced postoperative pain, morbidity, mortality, shorter hospital stay, shorter recovery time, lower costs, better life quality and incomparably better esthetic results. We hope that this benefits, first of all safety and effectiveness, will motivated neurologist to advocate VATS thymectomy at an early stage of MG and to encourage patients to accept this minimally invasive cosmetically acceptable approach in order to increase chances for complete stable remission.

***Fig. 6**. Postoperative wounds after VATS thymectomy.*

Sažetak

U poslednjih dvadeset godina minimalno invazivna video-asistirana torakoskopska hirurgija (VATS) je sve više prihvaćena hirurška tehnika u mnogim medicinskim centrima širom sveta koja se koristi za hirurško lečenje bolesnika sa mijastenijom gravis i predstavlja optimalan i bezbedan hirurški pristup za timektomiju.
Upravo je VATS timektomija najčešća indikacija kod ove bolesti.Ova hirurška tehnika u poređenju sa transsternalnim standardnim pristupima nudi rezultate koji pružaju prednost u manjoj traumi. To doprinosi boljem očuvanju plućne funkcije , manje izraženim bolovima i kraćem boravku u bolnici.
Estetski efekat je neuporedivo bolji.
Cilj ovog rada je da prikaže prednosti ove hirurške tehnike kao i da stimuliše lekare i pacijente da se što ranije odlučuju na hirurški tretman u lečenju mijastenije jer će to značajno doprineti poboljšanju simptoma i bržoj remisiji ove bolesti.

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