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Does repeat thymectomy improve symptoms in patients with refractory myasthenia gravis?

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Abstract

A best evidence topic in thoracic surgery was written according to a structured protocol. The question addressed was: Does repeat thymectomy improve symptoms in patients with refractory myasthenia gravis after thymectomy? A total of 189 papers were found using the reported search, of which seven represented the best evidence to answer the clinical question. The outcome measures included operative mortality and morbidity, as well as long-term remission rate. The authors, journal, date and country of publication, patient group studied, study type, relevant outcomes and results of these papers are tabulated. All the studies were small (4–21 patients), retrospective, single institutional case series. There was considerable heterogeneity in the studies. The interval between the first and second operation ranged from less than a year to over 10 years. The operative approach of the initial operation included transcervical, trans-sternal and substernal approaches. The maximal medical therapy received by the patients prior to reoperation varied from anticholinesterase alone to cytotoxic therapy and regular plasmapheresis. The severity of symptoms ranged from Osserman Class IIa to V. The operative approach to re-thymectomy included resternotomy, thoracoscopy and a combination of both. There was no perioperative mortality. One study reported injury to the innominate vein at resternotomy in 3 (14.3%) patients. One study reported myasthenic crisis in 2 patients in the postoperative period. Only one study reported complete remission in 2 patients. In general, however, 52–95% of patients reported some improvement. There was no consistent, objective measure of improvement in these studies. We conclude that repeat thymectomy for patients with refractory myasthenia gravis after previous thymectomy is safe especially for patients whose first procedure was transcervical. Complete remissions are rare but, in these small series, 60–70% of patients report improvement. Clinical improvement appears to be associated with the presence of residual thymic tissue at the second operation, but these cannot be reliably identified on preoperative imaging. Patient selection remains driven by symptoms.

Keywords: Review • Myasthenia gravis • Thymectomy • Reoperations

INTRODUCTION

A best evidence topic was constructed according to a structured protocol. This is fully described in the *ICVTS* [1].

THREE-PART QUESTION

In [patients with refractory myasthenia gravis symptoms despite previous thymectomy], does [repeat thymectomy] improve [disease severity]?

CLINICAL SCENARIO

A 30-year old female was referred to you with myasthenia gravis (MG) who underwent transcervical thymectomy 5 years earlier. She had Myasthenia Gravis Foundation of America (MGFA) Class IIIb symptoms which improved following surgery to Class IIb symptoms, but she recently required escalation of her medication. Computed tomography (CT) showed no obvious thymic tissue. You were asked to perform a re-thymectomy to ensure that all thymic remnants were removed. You remember being taught that more than a third of myasthenic patients do not benefit from a thymectomy; you find it difficult to believe that over a third of patients would have had incomplete resection. You then question whether there is a role for re-thymectomy in patients who failed to respond the first time. You resolve to check the literature yourself.

SEARCH STRATEGY

Medline 1950 to March 2013 using PubMed interface ('thymectomy' [MeSH Terms] OR 'thymectomy' [All Fields] OR re-thymectomy [All Fields]) AND myasthenia [All Fields] AND (severe [All Fields] OR refractory [All Fields]). The reference lists within the relevant publications were also searched.

Table 1: Best evidence papers

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Masaoka *et al.* (1982), Neurology, Japan [2] Case series (level 4)	Retrospective observational study: 6 cases of trans-sternal re-thymectomy following unsuccessful transcervical thymectomy 2–7.5 years earlier 5 patients were in Osserman Class IIb, and 1 in Class IIa 3 patients received steroid therapy Follow-up 5 years in 1 patient, 1 year 4 months or less in the remaining 5 patients	Pathology Clinical improvement	Residual thymus observed in all cases, mean 19.0 g 4 (60%) patients improved Patients who were already on steroids before surgery did not show improvement	Small number of patients The patients were not on maximal medical therapy Surgical approach and postoperative course not described Very short follow-up No definition for remission or improvement 'Response' did not take account of durability of improvement
Miller *et al.* (1991), Neurology, USA [3] Case series (level 4)	Retrospective case series: 6 patients, mean age 36, with severe, refractory, generalized MG despite previous thymectomy (4 trans-sternal, 1 transcervical and 1 substernal) after a mean of 8.9 years All patients received high-dose pyridostigmine, steroids and cytotoxic drugs. 5 patients required long-term maintenance plasma exchange (mean 2.4/month) In no patients was residual thymic tissue found on CT Mean follow-up of 6 years	Clinical improvement	There were no complete remissions 5 patients had significant improvement in bulbar and limb function requiring lower doses of corticosteroids and anticholinesterase. 4 of these patients were able to return to full-time productive activity, and the fifth was not able to due to his COPD The mean number of plasma exchange reduced from 2.4/month to 0.3/month Mean pyridostigmine dose reduced from 1290 to 270 mg/day. Mean prednisolone dose reduced from 51 to 18 mg/day. Cytotoxic drugs were discontinued in 3 patients	Small population Patients were on maximal medical therapy Follow-up adequately long Most patients experience clinically and functionally meaningful improvement
Rosenberg *et al.* (1983), Am J Med, Argentina [4] Case series (level 4)	Retrospective observational study: 24 patients who previously underwent transcervical thymectomy did not improve or only partially improved after a period ranging from 2 to 91 months 18 showed evidence of residual thymic tissue on pneumomediastinography, of which 13 underwent trans-sternal re-thymectomy Median follow-up of 11 months with 2 patients lost to follow-up	Clinical	No complete remissions 7 (64%) patients improved clinically: 5 on reduced medication and 2 required equal or higher doses	No information on clinical severity and medical treatment of operated patients Postoperative course was not described Follow-up period very short
Henze *et al.* (1984), Scand J Thorac Cardiovasc Surg, Sweden [5] Case series (level 4)	Retrospective observational study: 20 patients, mean age 23, with refractory MG despite transcervical thymectomy, who underwent trans-sternal re-thymectomy after a mean interval of 6 years 8 patients on medical immunosuppression	Postoperative course and complications Pathology	No mortality All patients had residual thymic tissue, 18 patients had intact lower thymic lobes and 1 had a thymoma	Only 8 (40%) patients received immunosuppression preoperatively, suggesting that they were not on maximal therapy Findings of grossly intact thymic lobes suggest that the primary operation was inadequate

Continued

Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
	None had evidence of thymic remnants on imaging Mean interval between operations 5.1 years Mean follow-up of 15 months	Clinical	19 (95%) patients improved Mean disability score fell from 8.2 to 4.9 ($P < 0.001$) Medical immunosuppression was discontinued in 6 of 11 patients, and reduced in 4 patients Anticholinesterase reduced to 67% preoperative dose ($P < 0.01$)	No definition of 'improvement'
Mineo *et al*. (1998), J Thorac Cardiovasc Surg, Italy [6] Case series (level 4)	Retrospective case series: 4 patients, mean age 41, with refractory non-thymomatous MG after a mean of 120 months after an initial thymectomy (3 transcervical and 1 partial sternotomy) underwent thoracoscopic re-thymectomy All required high-dose pyridostigmine (mean 560 mg/day) and steroids (mean 45 mg/day). One received azathioprine, and 3 required maintenance plasma exchanges (mean 6.25 exchanges per year) All patients had residual thymic remnants beneath the left innominate vein Mean follow-up of 15.0 months	Postoperative course and complications Remission rate	No mortality or major morbidity No complete remission 1 patient had a myasthenic crisis at 6 months 3 patients had improved Osserman class with reduction in steroid and pyridostigmine requirements 2 patients did not require further plasma exchange	Demonstrates the feasibility of re-thymectomy by VATS Significant improvement in very short follow-up
Pompeo *et al*. (2000), Ann Thorac Surg, Italy [7] Case series (level 4)	Retrospective case series: 8 patients, mean age 40.3 years, who underwent thoracoscopic completion thymectomy, a mean of 128 months after the initial operation. There were 2 Osserman Class II, 3 Class III and 3 Class IV patients Selection criteria: (i) lack of significant symptomatic improvement for at least 3 years after thymectomy, (ii) deterioration of symptoms lasting >24 months not controlled by maximal medical therapy, or requiring repeated exchange cycles (6 patients) and (iii) evidence of residual thymic tissue on CT or MRI Mean follow-up of 28.3 months	Postoperative course and complications Remission rate	No deaths 2 patients had myasthenic crisis requiring reintubation and ventilation. Did not specify which class these patients were from Mean hospital stay of 4.75 days There were no complete remissions 6 (75%) patients improved at least one class (mean Osserman class 3.77–2.12, $P = 0.03$) Reduced corticosteroid dosage (43 to 20 mg/day, $P = 0.03$). No significant changes in pyridostigmine, azathioprine or plasma exchange cycles All 3 Class IV patients improved, to Class I, II and III, respectively	An update on Mineo *et al*. [6] on VATS re-thymectomy, but still a very small study Patient selection based on refractoriness instead of severity, and therefore included 2 Class II patients The authors claimed residual thymic tissue on imaging as selection criteria, but the Mineo series [6] found no evidence of remnant on imaging
Zieliński *et al*. (2004), Interact CardioVasc Thorac Surg, Poland [8]	Retrospective case series: 21 patients, mean age 33.6 years, with refractory MG after thymectomy (1 left thoracotomy, 18 partial sternotomy and 1 trans-sternal extended thymectomy), undergoing	Postoperative course and complications	No early or late mortality 3 (14.3%) injury to the left innominate vein requiring repair	Definitions of improvement or deterioration not clear That only 66.7% patients were receiving steroids or

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Table 1: (*Continued*)

Author, date, journal and country Study type (level of evidence)	Patient group	Outcomes	Key results	Comments
Case series (level 4)	extended re-thymectomy using a novel video-assisted re-sternotomy technique Mean interval between the two operations was 6.4 years Mean Osserman Class (I–V) was 3.52 (range II–V) 14 (66.7%) patients received steroids or immunosuppressants, of which 4 (19%) received steroids Only 17 patients with a follow-up period of over 1 year were analysed. Mean follow-up of 3.4 years	Remission rate	No postoperative respiratory failure requiring a ventilator 2 of (11.8%) 17 patients had complete remission. A further 9 (52.9%) of 17 patients showed improvement. The rest showed no improvement, but none showed deterioration	immunosuppressants suggests that the patients were not on maximal medical therapy

SEARCH OUTCOME

One hundred and eighty-nine papers were found using the reported search. From these, seven papers were identified which provided the best evidence to answer the question. These are presented in Table 1.

RESULTS

Masaoka *et al.* [2] performed trans-sternal extended re-thymectomy in 6 patients who remained with Osserman Class II symptoms after previous transcervical thymectomy. They found thymic remnants beneath the left brachiocephalic vein in all cases. Four (67%) patients improved within a short median follow-up of 10.5 months, although medication requirements and degree of improvement were not reported.

Miller *et al.* [3] in 1991 reported trans-sternal re-thymectomy in 6 patients with severe myasthenia gravis despite previous thymectomy (4 trans-sternal, 1 transcervical and 1 substernal). All were on maximal medical therapy and 5 required long-term maintenance plasma exchange. No postoperative complications were reported. There was no complete remission after 6 years, but there was a substantial reduction in the medication dosage and plasma exchange cycles, while cytotoxic medication was discontinued in 3 patients.

Rosenberg *et al.* [4] reported trans-sternal re-thymectomy in 13 patients with persistent symptoms after previous transcervical thymectomy (7 partial recovery, 5 no improvement and 1 worse symptoms) and evidence of residual thymus on pneumomediastinography. Two patients were lost to follow-up. There were no complete remissions at a median follow-up of 11 months, but 7 (64%) patients reported improvement and 5 were on reduced medication.

Henze *et al.* [5] reported trans-sternal re-thymectomy in 20 patients with generalized, disabling symptoms, which did not improve after transcervical thymectomy after a mean of 6.5 years. While preoperative imaging failed to demonstrate thymic remnants, at operation all had residual thymic tissue and 18 were intact encapsulated thymic lobes. This suggested that the primary operation was incomplete. There was no mortality. At a mean follow-up of 15 months, 19 (95%) patients improved, mean disability score fell (8.2 vs 4.9, $P < 0.001$), anticholinesterase dose reduced 67% ($P < 0.01$) and medical immunosuppression was discontinued in 6 of 11 patients and reduced in 4.

Mineo *et al.* [6] described re-thymectomy using the video-assisted thoracoscopic surgery (VATS) approach in 1998. He reported 4 patients with severe myasthenia gravis on maximal medical therapy (including 3 on regular plasma exchanges) who did not improve after a previous thymectomy (3 transcervical and 1 trans-sternal). In none was there evidence of residual thymic tissue on CT/magnetic resonance imaging (MRI). There was no mortality or major morbidity. There were no complete remissions, but 2 patients did not need further plasma exchange, and 3 had improvement in their Osserman class.

Pompeo *et al.* [7] updated this series to 8 patients in 2000. There were no deaths, but 2 patients required reintubation for myasthenic crisis. After a mean follow-up of 28.3 months, there was no complete remission, but 6 (75%) patients improved at least one Osserman class and all Class IV patients improved. The mean prednisolone dose reduced from 43 to 20 mg ($P = 0.03$), but pyridostigmine and azathioprine doses or plasma exchange frequency did not change significantly. All the 5 patients who had gross thymic tissue removed improved.

Zieliński *et al.* [8] described resternotomy re-thymectomy in 21 patients with a mean Osserman class of 3.52 using a novel video-assisted re-sternotomy technique. Only 14 (67%) patients received steroids, suggesting that they were not on maximal medical therapy. In 4 (19%) patients, no thymic tissue was found. There were 3 (14.3%) cases of injury to the innominate vein requiring repair, but no mortality or respiratory failure requiring ventilation. Seventeen patients with a follow-up of over a year, a

mean follow-up of 3.4 years, were analysed. Two (11.8%) achieved complete remission, 9 (52.9) showed improvement and none showed deterioration. Six (50%) of the 12 patients on steroids or immunosuppressive medication preoperatively were able to discontinue them.

CLINICAL BOTTOM LINE

Repeat thymectomy for patients with refractory myasthenia gravis after previous thymectomy is safe especially for patients whose first procedure was transcervical. Complete remissions are rare, but 60–70% patients report improvement. Clinical improvement appears to be associated with the presence of thymic tissue, but these cannot be reliably identified on preoperative imaging. Patient selection remains driven by symptoms.

Conflict of interest: none declared.

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