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[Intervention Review]

Thymectomy for non-thymomatous myasthenia gravis

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ABSTRACT

Background

Treatments currently used for patients with myasthenia gravis (MG) include steroids, non-steroid immune suppressive agents, plasma exchange, intravenous immunoglobulin and thymectomy. Data from randomized controlled trials (RCTs) support the use of some of these therapeutic modalities and the evidence for non-surgical therapies are the subject of other Cochrane reviews. Significant uncertainty and variation persist in clinical practice regarding the potential role of thymectomy in the treatment of people with MG.

Objectives

To assess the efficacy and safety of thymectomy in the management of people with non-thymomatous MG.

Search methods

On 31 March 2013, we searched the Cochrane Neuromuscular Disease Group Specialized Register, CENTRAL (2013, Issue 3), MEDLINE (January 1966 to March 2013), EMBASE (January 1980 to March 2013) and LILACS (January 1992 to March 2013) for RCTs. Two authors (RS and GC) read all retrieved abstracts and reviewed the full texts of potentially relevant articles. These two authors checked references of all manuscripts identified in the review to identify additional articles that were of relevance and contacted experts in the field to identify additional published and unpublished data. Where necessary, authors were contacted for further information.

Selection criteria

Randomized or quasi-randomized controlled trials of thymectomy against no treatment or any medical treatment, and thymectomy plus medical treatment against medical treatment alone, in people with non-thymomatous MG.

We did not use measured outcomes as criteria for study selection.

Data collection and analysis

We planned that two authors would independently extract data onto a specially designed data extraction form and assess risk of bias; however, there were no included studies in the review. We would have identified any adverse effects of thymectomy from the included trials.

Main results

We did not identify any RCTs testing the efficacy of thymectomy in the treatment of MG. In the absence of data from RCTs, we were unable to do any further analysis.

Authors' conclusions

There is no randomized controlled trial literature that allows meaningful conclusions about the efficacy of thymectomy on MG. Data from several class III observational studies suggest that thymectomy could be beneficial in MG. An RCT is needed to elucidate if thymectomy is useful, and to what extent, in MG.

PLAIN LANGUAGE SUMMARY

Surgical removal of the thymus for myasthenia gravis that is not caused by a tumour of the thymus

Myasthenia gravis is a disorder that causes muscle weakness and excessive muscle tiredness. In most people with myasthenia gravis, muscles throughout the body are affected in the first two years after the onset of symptoms, although there is also a form of the disease that affects only the eyes (ocular myasthenia). Myasthenia gravis occurs when the person's own immune system attacks the vital structures that transmit impulses from nerves to muscle, the neuromuscular junctions. A tumour affecting an immune system organ called the thymus (a thymoma) is sometimes the underlying cause; this is known as thymomatous myasthenia gravis. Thymomatous myasthenia gravis was not the subject of this systematic review as the thymoma should be treated on its own merit, independently of the myasthenia gravis.

Some observational studies suggest that removal of the thymus (thymectomy) might be useful in people with myasthenia gravis who do not have a thymoma (non-thymomatous myasthenia gravis). It is generally accepted that thymectomy should not be used in ocular myasthenia, although some people think that it could be used when there is no response to medical therapy. In our systematic review of the evidence we did not find any randomized controlled trials (RCTs) of thymectomy in non-thymomatous myasthenia gravis. At present, as there is no RCT, the value of thymectomy is a subject of controversy and medical practice varies among practising physicians. An RCT is required to find out whether thymectomy is effective in generalized myasthenia gravis.

BACKGROUND

Description of the condition

Myasthenia gravis (MG) was first described in the medical literature by Thomas Willis, an English physician, in the book "De anima brutorum" in 1672. The term 'myasthenia gravis', from Greek 'myasthenia', meaning muscle weakness, and Latin 'gravis', for severe, was first used by Friedrich Jolly in 1895 (Hughes 2005). It is in some ways a misleading term as not all patients suffering MG have a life threatening condition. Even though MG is a rare chronic disease, it is the most common disorder of the neuromuscular junction. Prevalence rates range from 0.5 to 20.4 per 100,000 (Phillips 2003). Despite its rarity it imposes a heavy financial burden on society and for affected individuals. It commonly affects young females. There is, however, a second peak of incidence after the fifth decade of life, which seems to be increasing (Casetta 2010) and which has a stronger association with thymoma (Monden 1984). In some populations this second peak affects mainly men but in other populations men and women are equally affected (Aarli 1999), or women remain the most affected group (Matsuda 2005).

MG was the first neurological disease to be described as antibody mediated (Vincent 2002). Its pathology is the result of an autoimmune attack on the neuromuscular junction (Kaminski 2003), the nicotinic acetylcholine receptor (AChR) located on the postsynaptic surface of the neuromuscular junction being its primary antigenic target (Vincent 2001). AChR antibodies, which interfere with neuromuscular transmission, are detected in about 90% of people with generalized MG and 50% of patients with disease restricted to the ocular muscles (ocular myasthenia). A muscle specific receptor tyrosine kinase (MusK) has been proposed as another antigenic target in AChR negative MG (Evoli 2003; Vincent 2003). This anti-MusK positive MG is not believed to be

related to thymus abnormalities (Evoli 2003; Meriggioli 2009). Recently another autoantibody has been identified in AChR and MusK negative MG, targeting the low-density lipoprotein receptor-related protein 4 (LRP4) (Higuchi 2011; Pevzner 2012).

Clinically, MG is a heterogeneous condition that is characterized by variable and sometimes asymmetrical weakness and easy muscle fatigability of the ocular, bulbar, trunk and limb muscles (Newsom-Davis 2001). Any voluntary muscle can be involved, but there is a high and distinct propensity to involve the extrinsic ocular muscles, causing eyelid ptosis and diplopia or double vision. Most studies agree that ocular symptoms are the first manifestation of MG in about 50% of patients (Bever 1983). Among those patients presenting with ocular symptoms, 50% to 60% will develop generalized muscle weakness of different degrees in the first two years after presentation (Bever 1983; Beekman 1997). On the other hand, about 10% of patients with MG initially present with bulbar symptoms, 10% with limb involvement and 30% with generalized muscle weakness. About 30% of purely ocular MG patients will go into complete remission, and about 10% of generalized MG patients will also go into remission within 10 years from onset (Oostertihuis 1982; Grob 1987). The prognosis of MG has changed from a disease that had a mortality of about 33%, after the introduction of anticholinesterases (Grob 1987), to a life expectancy only slightly reduced compared to the general population (Christensen 1998). Today, most people with MG achieve a good quality of life. Generalized MG, when associated with predominant bulbar muscle weakness, however, is a disease that imposes severe restrictions on people's daily life and when severe can produce a myasthenic crisis or require ventilatory support. It is said that one in five patients with MG will develop one or more myasthenic crises, usually in the first two years of the disease (Oosterhuis 1989).

Generalized MG is treated with anticholinesterases and prednisone. Immunosuppressant drugs, such as azathioprine, ciclosporin, cyclophosphamide, or mycophenolate mofetil, are usually added when high doses of prednisone are needed to control the disease or the response is unsatisfactory. Azathioprine is the most frequently used immunosuppressant due to its good tolerance and there is good evidence for its efficacy in reducing the need for prednisone (Palace 1998). Ciclosporin has also proved to be efficacious in controlled trials, alone or in conjunction with prednisone (Tindall 1993). Rituximab, a chimeric monoclonal antibody against the protein CD20, which is primarily found on the surface of B cells, has also been anecdotally used in MG patients but its efficacy and safety are still under study (NCT00619671; NCT00774462). Plasmapheresis and intravenous immunoglobulin (IVIg) have been used successfully in the treatment of myasthenic acute deterioration and myasthenic crisis, although good quality evidence is scarce (Gajdos 2002; Gajdos 2008). Besides medical treatment, thymectomy has been used for many years in conjunction with steroids or other immunosuppressants as a long-term treatment (Pascuzzi 1984).

Description of the intervention

Thymectomy is the surgical removal of the thymus, and a number of different surgical approaches have been used. The three primary ones are transcervical, transsternal, and videoscopic (Jaretzki 2000). Within each approach there are variations in the extent of the resection of the thymus. The transsternal approach, especially the extended transsternal operation, is the most commonly employed. The transcervical and videoscopic techniques have been developed to reduce morbidity from the surgery and to avoid scars. However, controversy exists about the maximum degree of resection achieved with the different methods and over the benefits for people with MG. Complications have been significantly reduced; mortality rates are now below 1% and the most common morbidities include acute respiratory failure from MG crisis (6%), infection (11%), and recurrent laryngeal or phrenic nerve injury (0% to 2%) (Gronseth 2000).

Thymectomy was first used in MG in 1913, when Sauerbruch reported a patient with thyroid disease in which the removal of the thymus resulted in improvement of myasthenia, but the patient died shortly afterwards due to a mediastinal infection. In 1939, Bladlock reported a long-lasting improvement of MG after excision of a thymoma. Since then, thymectomy has frequently been used in generalized MG without thymoma, but its benefit in the management of non-thymomatous MG has not been resolved (Sonett 2008). A number of case series and anecdotal reports (class III and IV) claim net benefit using this procedure (Gronseth 2000). This uncertainty and the successful use of immunosuppressants have cast doubts on the role of thymectomy in the management of MG. A survey that included 56 experts found that only three expressed no reservation in using thymectomy in generalized MG, and more than 20% had significant reservations about recommending this procedure (Lanska 1990). These facts have resulted in wide variation in clinical practice. The aim of this Cochrane systematic review is to identify randomized controlled trials (RCTs) of this surgical intervention for patients suffering from non thymomatous MG that may help in clarifying this issue.

How the intervention might work

The role of the thymus in the pathogenesis of MG has not been fully elucidated, but its association is suggested by empirical and physiopathological evidence. Much of this evidence suggests that the thymus is implicated in the genesis of MG and also that thymectomy may reduce the severity of MG by reducing autoimmune activity (Penn 1994; Kaminski 2003). As early as 1892, Herman Hoppe, in the USA, reported the association between MG and thymoma. About 70% of MG patients have lymphoid follicular hyperplasia of the thymus and about 10% have a thymoma. An increased number of germinal centres in a patient with MG was first described in 1900 (Buzzard 1905), and T-cell lines that are specific for AChR can be cloned from the thymus (Melms

1988). The medulla of the thymus contains muscle-like cells that express AChR on their surface (Schluep 1987) and also epithelial cells that can express AChR in transgenic mice (Salomon 1998). Therefore, thymectomy in patient with non-thymomatous MG could remove a key element in the genesis of the autoimmune response. The removal of the thymus could thus eliminate the main source of production of B lymphocytes able to produce antibodies to the AChR; these antibodies usually decrease in people with MG after thymectomy (Kuks 1991).

Why it is important to do this review

Therapies available for patients with MG include corticosteroids, plasma exchange, IVIg, other immune suppressive agents, and thymectomy. The data supporting the efficacy of corticosteroids (Schneider-Gold 2005), non-corticosteroid immune suppressive agents (Hart 2007), plasma exchange (Gajdos 2002), acetylcholinesterase inhibitors (Mehndiratta 2011), and IVIg (Gajdos 2008) have been addressed in prior Cochrane reviews. A number of case series and anecdotal reports claim net benefit for the use of thymectomy in people with MG (McQuillen 1977). The evidence supporting the use of thymectomy as a treatment for patients with myasthenia, however, has not previously been the topic of a Cochrane review, although much of the data were reviewed several years ago in a Practice Parameter published by the Quality Standard Subcommittee of the American Academy of Neurology (Gronseth 2000). The evidence included in that report was based on a limited literature search, only of publications included in the National Library of Medicine's MEDLINE database, and included non-randomised trials. Gronseth and Barohn concluded that the available data suggested an association between thymectomy and improvement or remission of MG, but cautioned that the observed benefits could be "merely a result of the multiple differences in baseline characteristics between the surgical and non surgical groups" (Gronseth 2000). As a consequence, the role of thymectomy in the management of MG is still under dispute and there is great variation in clinical practice (Lanska 1990). One RCT is currently under way to definitively address the benefits of thymectomy, both with respect to symptom control and to a steroid-sparing effect (NCT00294658).

OBJECTIVES

To assess the efficacy and safety of thymectomy in the management of people with non-thymomatous MG.

METHODS

Criteria for considering studies for this review

Types of studies

We aimed to include in the review all RCTs and quasi-RCTs in people with non-thymomatous MG. We planned to comment on the results from good-quality observational studies (case-control and cohort studies) in the Discussion.

Types of participants

This review included participants with non-thymomatous autoimmune MG, both ocular and generalized forms, as defined by the Myasthenia Gravis Foundation of America (MGFA) classification. Ocular MG is defined as any ocular muscle weakness, including weakness of eye closure, but all other muscles are normal. Generalized MG is defined as weakness of any other skeletal muscle other than ocular, and the ocular muscle may be involved. We included both children and adults.

Types of interventions

We considered thymectomy in all its modalities: transsternal, extended transsternal, suprasternal, laparoscopic, and video-assisted thoracoscopic thymectomy. We aimed to compare thymectomy against: (1) any other available medical treatments used to treat MG, (2) no treatment, or (3) sham surgery. We aimed to include: (1) trials evaluating the efficacy of thymectomy, applied as an isolated procedure, against medical treatment, and (2) trials evaluating thymectomy used in conjunction with some form of medical treatment (such as corticosteroids or immunosuppressants) against medical treatment alone.

Types of outcome measures

We selected the following as outcomes of interest within studies eligible for the review. We did not use outcomes as part of the study selection criteria.

Primary outcomes

Improvement in myasthenic weakness within 12 months of thymectomy. We had planned to rely on each individual study's method for evaluating improvement of myasthenic weakness.

Secondary outcomes

1. Reduction by at least one third in the dose of corticosteroids within 12 months of thymectomy, irrespective of the method used for assessing the dosage so long as it was consistent and clear.
2. Improvement in quality of life (QoL) at 12 months or more after thymectomy, as measured by the Short Form (SF)-36, the

Individualized Neuromuscular Quality of Life (INQoL) scale (Vincent 2007), the MG-QoL-15 (Burns 2008), or any other validated measure of QoL.

3. Pharmacological or complete remission, as defined by the Myasthenia Gravis Foundation of America (MGFA) (Jaretzki 2000).
4. Death during three years of follow-up.
5. Adverse events during three years of follow-up.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Neuromuscular Disease Group Specialized Register (31 March 2013), CENTRAL (2013, Issue 3), MEDLINE (January 1966 to March 2013), EMBASE (January 1980 to March 2013), and LILACS (January 1982 to March 2013). The detailed search strategies are listed in the appendices: CENTRAL (Appendix 1), MEDLINE (Appendix 2), EMBASE (Appendix 3), and LILACS (Appendix 4).

Earlier searches for this review (up to November 2011) were based on the MEDLINE strategy in the published protocol (Cea 2009). The original strategy was revised by the Cochrane Neuromuscular Disease Group Trials Search Co-ordinator because it could have excluded relevant studies.

Searching other resources

Two review authors (GC, RS) read the abstracts of all articles retrieved for potential relevance to the review and read in full any articles that were definitely or possibly relevant. We also reviewed the bibliographies of the articles obtained in this way in order to identify additional studies. We contacted experts in the field in order to identify any further published or unpublished studies that might be relevant to the review.

Data collection and analysis

Selection of studies

Two review authors (RS and GC) independently reviewed the titles and abstracts of all articles in order to identify studies that might be relevant. The authors made a decision regarding their suitability for inclusion in the review based on whether they met pre-specified inclusion criteria. To be included in the review, studies had to be RCTs (or quasi-RCTs) comparing: (a) thymectomy alone versus placebo, no treatment or some other treatment; or (b) thymectomy in conjunction with other medical treatment against medical treatment alone. Disagreement between the two authors was resolved by discussion. Review authors were not blinded to trial authors' names, institutional affiliations, or journals of publication.

Data extraction and management

We planned that two review authors would independently extract data onto a specially designed data extraction form (Higgins 2011b). One author would enter data into the Cochrane software Review Manager (RevMan) and a second author would check the data entry. We would resolve any disagreements by discussion.

Assessment of risk of bias in included studies

We planned that two review authors would independently assess the risk of bias in the included trials according to the guidance in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011a). We would have paid attention to: the randomization of participants including allocation concealment and generation of randomization sequence; blinding of participants and investigators; blinding of outcome assessors; incomplete outcome data including loss to follow-up and use of intention-to-treat analysis; selective outcome reporting; and any other source of bias not covered by other domains, such as whether the groups were treated equally other than application of the intervention, and baseline imbalance.

We would have tested publication bias using funnel plots or other corrective analytical methods, depending on the number of clinical trials included in the systematic review.

Measures of treatment effect

We would have expressed both primary and secondary outcomes as dichotomous, as all our outcomes allow a yes or no answer. We would have used the Cochrane Review Manager (RevMan) statistical software to calculate risk ratios for dichotomous data, and mean differences for continuous data, both with 95% confidence intervals.

Dealing with missing data

The intent was to analyze only the available data, ignoring missing data. However, the issue is moot since no RCT data were identified.

Assessment of heterogeneity

We would have assessed heterogeneity among trials using the I^2 statistic and Chi^2 test in RevMan 5 to help in identifying statistical heterogeneity as well as looking at the visual forest plots. We would have used a fixed-effect model in the primary analysis.

Data synthesis

We would have calculated a weighted treatment effect across trials using RevMan 5.

Summary of findings table

If, in future, trials become available we will include a 'Summary of findings' table following the guidance in Chapter 11 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Schünemann 2011). The table will provide information on the quality of evidence according to the GRADE approach and the magnitude of effect for all our outcomes, as listed in Table 1.

Subgroup analysis and investigation of heterogeneity

We planned subgroup analysis for different groups of participants: children (under 14 years old) and adults; ocular and generalized MG. We would have considered all forms of thymectomy together for our primary analysis but would have also performed separate analyses for laparoscopic and open thymectomy.

We would have investigated sources of heterogeneity, for example by repeating the analysis after elimination of trials that scored poorly on individual items of the 'Risk of bias' criteria, or by thoroughly assessing qualitative differences among included trials.

RESULTS

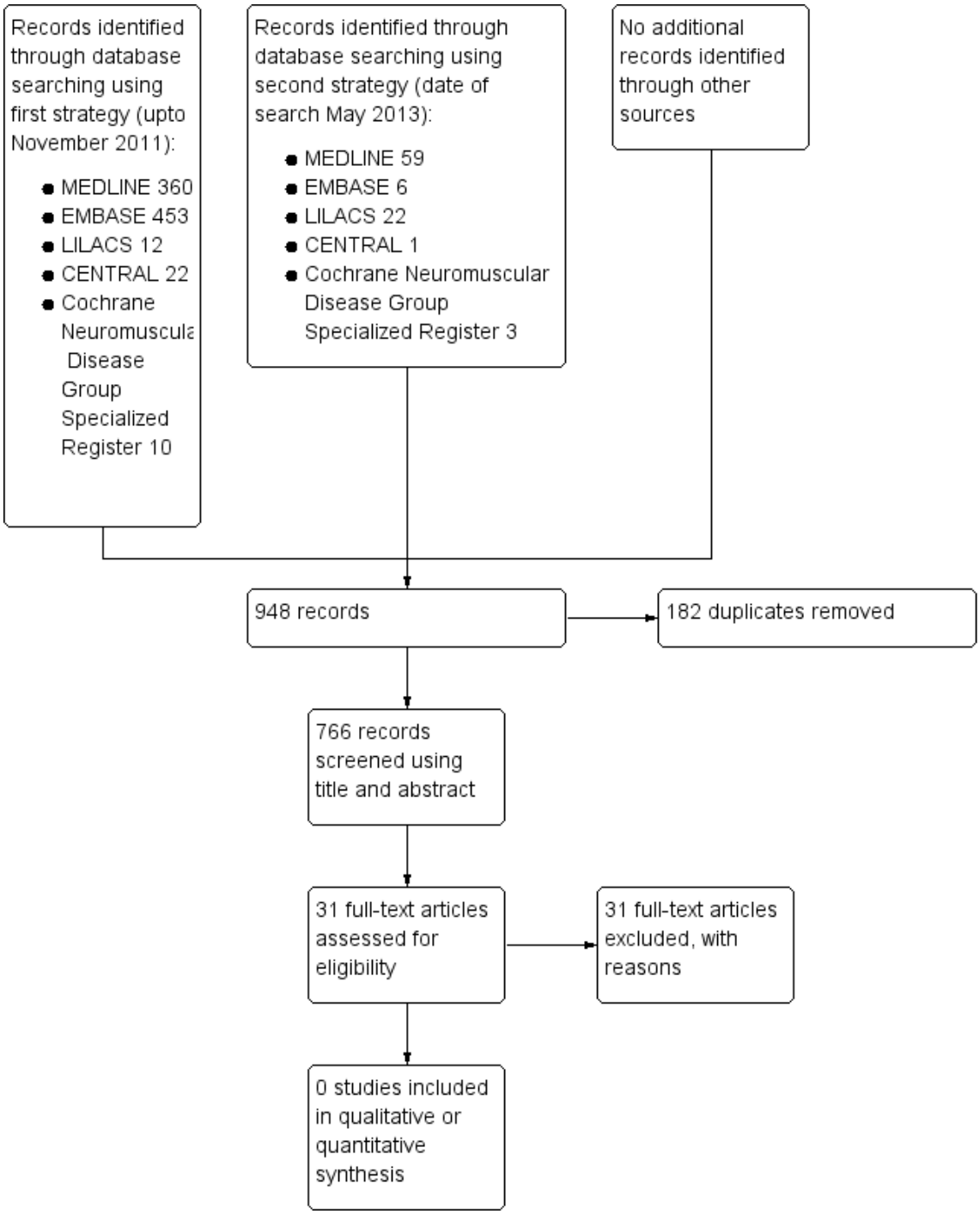
Description of studies

Results of the search

Our original searches (date of search November 2011), based on the strategy in the published protocol, retrieved 360 articles in MEDLINE, 453 in EMBASE, 12 in LILACS, 22 in CENTRAL, and 10 in the Specialized Register. The electronic literature searches in March 2013 yielded 59 additional articles in MEDLINE, six in EMBASE, 22 in LILACS, one in CENTRAL, and three in the Cochrane Neuromuscular Disease Group Specialized Register.

Two review authors read the full texts of 31 studies but none of them met our inclusion criteria. The study selection process is shown in Figure 1. We found one ongoing RCT on thymectomy in MG (NCT00294658), see below and in Ongoing studies.

Figure 1. Study flow diagram.



Included studies

We identified no RCTs for inclusion in this review. We identified one ongoing RCT (NCT00294658) in which thymectomy is compared, in a blind fashion, with medical treatment for a period of three years. The study includes patients older than 18 years and younger than 65 years, with MG of less than five years' duration, who are not taking immunosuppressants other than prednisone, who are classified as stage II to IV according to the MGFA classification, and who have positive AChR antibodies.

Excluded studies

We identified several observational descriptive studies, including a large series of thymectomized patients. Most of these were retrospective or prospective with no explicit follow-up protocol. Some of them enrolled patients during a span of time in which medical practice experienced considerable improvements in anesthesia, intensive care, and drugs for the control of immune activity, hampering any meaningful conclusion on the effectiveness of thymectomy. The lack of methodological rigor and the almost exclusively descriptive character of the published reports contributed to this difficulty (Grimes 2002).

We found three studies (Buckingham 1976; Werneck 1991; Soleimani 2004) in which a methodology resembling a retrospective cohort study was used. There was, however, no clear indication in the methodology that the data were obtained following the main requirement for this type of research design, namely that the exposed and control participants were chosen before knowing their outcomes (Riegelman 2005).

Risk of bias in included studies

Not applicable

Effects of interventions

We found no RCTs of thymectomy for non-thymomatous myasthenia gravis.

DISCUSSION

This systematic review identified no RCTs involving surgical treatment of MG, either ocular or generalized, even though a thorough search was conducted, including a mail survey addressed to the main researchers in this area. The international multicenter prospective randomized trial 'Thymectomy in non-thymomatous MG patients receiving prednisone' (NCT00294658) appeared to be the only trial likely to provide analyzable data, once completed.

This review did not find properly designed analytical observational studies (case-control or cohort studies) relevant to this review (Grimes 2002). We found several case series addressing the issue of thymectomy in the management of MG, most of them retrospective. Several included thymoma in their description and many used different surgical techniques, analyzing them as a homogeneous group. Some compared their case series with historical controls or with patients not eligible for surgery, or who rejected surgery, exposing the findings to inadmissible bias. Most of these reports acknowledged the limited scope of their conclusions because the design of their studies was not randomized. In addition, appropriate outcomes and assessments for judging treatment success in this condition have only been recently agreed (Jaretzki 2000).

We found three studies that resembled retrospective cohort studies. One of the studies (Soleimani 2004) included patients with thymoma, and did not report data on the outcomes considered in our review. They found a significant decrease in the proportion of patients suffering myasthenic crisis among those undergoing thymectomy compared with the non-surgical group, but the validity of these results was hampered by a non-conventional definition of the outcome (Bedlack 2002) and the reliance on routinely collected data from the medical records and not from a customized form (Reeves 2011). The second study (Kawaguchi 2007) found a non-significant greater percentage of clinical remissions in the thymectomized group compared to the non-thymectomized group, but provided incomplete data on both the characteristics and outcomes of medically and surgically treated patients. This study relied, also, on information obtained from routinely collected data registered in medical records and not from a customized form. The third study (Buckingham 1976) found an increased proportion of remissions and a decreased number of deaths caused by MG among patients undergoing thymectomy, but it included in the analysis only a minor proportion of the medically treated patients, matched by age, sex, and severity of the disease, with 80 of the 104 patients undergoing surgery. The authors did not report adequate data on the patients excluded from both cohorts.

As we found no RCTs, the only potential biases affecting this review are those related to ignoring either unpublished or published trials existing in non-indexed journals. Nonetheless, we considered this very unlikely as this review included a thorough search strategy, including direct contact with key opinion leaders in this subject who most likely should be aware of any RCT that was unpublished or published in gray literature.

A practice parameter on the use of thymectomy for autoimmune

MG was published in 2000 by the American Academy of Neurology (AAN) (Gronseth 2000). This review used a restricted search strategy (MEDLINE and references from identified articles). No RCT was found and the observational studies included in the review qualified as class III evidence according to the parameters published by the AAN in 2008 (French 2008). The poor quality of the evidence included in the review hampers any meaningful conclusion on the efficacy of thymectomy for autoimmune MG.

Implications for research

There is a need for well-designed randomized, controlled studies or properly designed prospective cohort studies to determine the efficacy of thymectomy in non-thymomatous myasthenia gravis. We identified an ongoing randomized controlled trial evaluating the use of thymectomy in non-thymomatous myasthenia gravis patients receiving prednisone therapy (MGTX), and the results are expected for 2015.

AUTHORS' CONCLUSIONS

Implications for practice

Thymectomy, as part of the management of myasthenia gravis, is the subject of controversy and considerable variation in clinical practice. In the absence of any published randomized or quasi-randomized trials, the objective evidence for the use of thymectomy in non-thymomatous myasthenia gravis is weak.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Beekman 1997	Retrospective case series
Beghi 1991	Retrospective case series
Buckingham 1976	Retrospective cohort type study
Donaldson 1990	Retrospective case series
Durelli 1991	Retrospective case series
Eaton 1955	Retrospective case series and narrative review
Edwards 1972	Retrospective case series
Emeryk 1976	Retrospective case series
Grob 1987	Retrospective case series
Henson 1965	Retrospective case series
Kawaguchi 2007	Retrospective cohort type study
Mack 1996	Retrospective case series
Manlulu 2005	Restrospective case series
Mantegazza 1990	Retrospective case series
McQuillen 1977	Narrative review published as guest editorial
Molly 2009	Retrospective case series
Olanow 1987	Retrospective case series
Oosterhuis 1981	Retrospective case series
Papatestas 1987	Retrospective case series
Perlo 1971	Retrospective case series
Roberts 2001	Retrospective case series

(*Continued*)

Rodriguez 1983	Retrospective case series
Romi 2003	Retrospective case series
Savcenko 2002	Retrospective case series
Scadding 1985	Retrospective case series
Simpson 1958	Retrospective case series
Soleimani 2004	Retrospective cohort type study
Tellez-Zenteno 2001	Retrospective case series
Werneck 1991	Retrospective case series
Yim 1995	Retrospective case series
Zeldowicz 1969	Retrospective case series

Characteristics of ongoing studies *[ordered by study ID]*

NCT00294658

Trial name or title	A multicenter, single-blind, randomized study comparing thymectomy to no thymectomy in non-thymomatous myasthenia gravis (MG) patients receiving prednisone
Methods	Blinded RCT
Participants	Patients older than 18 years and younger than 65 years, with less than five years of MG, classified in stage II to IV according to the classification of the MGFA, with positive AChR antibodies, not taking immunosuppressants other than prednisone
Interventions	Thymectomy
Outcomes	Primary: Stage 1: Comparison of the prednisone protocol alone to prednisone protocol plus thymectomy, based on the clinical response to therapy measured over the 3 year trial period by the **A**rea **U**nder the **Q**uantitative **M**yasthenia **G**ravis (QMG) weakness score (AUQMG) Stage 2: Testing the difference in the total prednisone used over the 3-year trial period measured by pill count from blister packs **A**rea **U**nder the prednisone **D**ose **T**ime **C**urve, (AUDTC), conditional on the results of comparing AUQMG Secondary: Frequency of treatment-associated complications and treatment-associated symptoms questionnaire score; Change in QMG and MG-ADL over time and at M12, M24 and M36; time from month 0 to reach initial Minimal Manifestation (MM) status; MM status at M12, M24 and M36; actual prednisone dose at M36;

NCT00294658 (*Continued*)

	quality of life assessment (SF-36) at M12, M24 and M36; cumulative days in hospital for treatment of, or complications related to, MG by M24 and M36; number of plasmaphereses and IVIg infusions, and total dose of IVIg from M0 to M36
Starting date	2006
Contact information	Gury Cutter and Greg Minisman
Notes	

ADL: activities of daily living
IVIg: intravenous immunoglobulin
MG: myasthenia gravis
MGFA: Myasthenia Gravis Foundation of America (MGFA)
QMG: Quantitative Myasthenia Gravis score
RCT: randomized controlled trial
SF-36: Short Form-36 Health Survey

DATA AND ANALYSES

This review has no analyses.

ADDITIONAL TABLES

Table 1. Outcomes for a 'Summary of findings' table

Thymectomy compared with non surgical treatment for myasthenia gravis
Patient or population: patients with non-thymomatous myasthenia gravis **Settings:** inpatients and outpatients **Intervention:** thymectomy **Comparison:** any other available medical treatments used to treat MG, no treatment, or sham surgery
Outcomes
Improvement in myasthenic weakness within 12 months of thymectomy
Reduction by at least one third in the dose of corticosteroids within 12 months of thymectomy
Improvement in quality of life at 12 months or more after thymectomy
Pharmacological or complete remission, as defined by the Myasthenia Gravis Foundation of America (MGFA)
Death during three years of follow-up
Adverse events during three years of follow-up

APPENDICES

Appendix 1. CENTRAL search strategy

#1 thymectom*
#2 "non thymomatous" near myastheni*
#3 (without near thymoma) and myastheni*
#4 "not associated with thymoma" and myastheni*
#5 #2 or #3 or #4
#6 #1 and #5

Appendix 2. MEDLINE (OvidSP) strategy

Database: Ovid MEDLINE(R) <1946 to March Week 3 2013>
Search Strategy:
---
1 randomized controlled trial.pt. (343749)
2 controlled clinical trial.pt. (85478)
3 randomized.ab. (246632)
4 placebo.ab. (136427)
5 drug therapy.fs. (1590966)
6 randomly.ab. (176808)
7 trial.ab. (253988)
8 groups.ab. (1151170)
9 or/1-8 (2968418)
10 exp animals/ not humans.sh. (3784285)
11 9 not 10 (2522067)
12 Thymectomy/ (6971)
13 thymectom$.tw. (5880)
14 12 or 13 (8881)
15 (non?thymom* adj3 myastheni*).mp. (47)
16 ((without adj3 thymom$) and myastheni$).mp. (188)
17 15 or 16 (230)
18 11 and 14 and 17 (59)
19 remove duplicates from 18 (59)

Appendix 3. EMBASE (OvidSP) strategy

Database: Embase <1980 to 2013 Week 13>
Search Strategy:
---
1 crossover-procedure.sh. (36535)
2 double-blind procedure.sh. (113825)
3 single-blind procedure.sh. (17167)
4 randomized controlled trial.sh. (339521)
5 (random$ or crossover$ or cross over$ or placebo$ or (doubl$ adj blind$) or allocat$).tw,ot. (942309)
6 trial.ti. (142943)
7 or/1-6 (1074052)
8 (animal/ or nonhuman/ or animal experiment/) and human/ (1249164)
9 animal/ or nonanimal/ or animal experiment/ (3371230)
10 9 not 8 (2789523)
11 7 not 10 (985119)
12 limit 11 to embase (769918)
13 thymectomy/ (7554)
14 thymectom$.tw. (6011)
15 13 or 14 (9129)
16 (non?thymom* adj3 myastheni*).mp. (61)
17 ((without adj3 thymom$) and myastheni$).mp. (222)
18 16 or 17 (279)
19 12 and 15 and 18 (6)

Appendix 4. LILACS strategy

((thymectomy or timectomia) and ((”not associated with thymoma“ or ”without thymoma“ or ”non thymomatous“) and myastheni$)) and ((PT:”Randomized Controlled Trial“ or ”Randomized Controlled trial“ or ”Ensayo Clínico Controlado Aleatorio“ or ”Ensaio Clínico Controlado Aleatório“ or PT:”Controlled Clinical Trial“ or ”Ensayo Clínico Controlado“ or ”Ensaio Clínico Controlado“ or ”Random allocation“ or ”Distribución Aleatoria“ or ”Distribuição Aleatória“ or randon$ or Randomized or randomly or ”double blind“ or ”duplo-cego“ or ”duplo-cego“ or ”single blind“ or ”simples-cego“ or ”simples cego“ or placebo$ or trial or groups) AND NOT (B01.050$ AND NOT (humans or humanos or humanos)))

CONTRIBUTIONS OF AUTHORS

RS and GC participated in the review of the literature, selected potentially relevant articles, and manually searched potentially relevant articles for further references, applied the inclusion criteria to these selected articles and wrote the review. MB and RV read the review and made contributions to the content and form of the review.

DECLARATIONS OF INTEREST

MB and GC are site investigators in the ongoing National Institute of Neurological Disorders and Stroke (NINDS)-funded RCT comparing thymectomy to no thymectomy in non-thymomatous myasthenia gravis patients receiving prednisone. RV is a blinded evaluator for the same trial. RS has no conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- None, Not specified.

External sources

- None, Not specified.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

The background information has been expanded.

The search strategies were revised as noted in the methods.

The ’Assessment of risk of bias in included studies’ and data extraction sections of the methods have been updated in accordance with the version of the *Cochrane Handbook for Systematic Reviews of Interventions* current at the time of writing (Higgins 2011a).

We clarified in the text that outcomes were not among our study selection criteria.

We specified outcomes that will be included in any ’Summary of findings’ table presented in a future update.

INDEX TERMS

Medical Subject Headings (MeSH)

*Thymectomy; Myasthenia Gravis [etiology; *surgery]

MeSH check words

Humans