Authors' objectives
To develop evidence-based recommendations for clinicians considering thymectomy for patients with nonthymomatous autoimmune myasthenia gravis (MG), by performing a systematic review and analysis of the literature.

Searching
The authors searched MEDLINE from 1966 to February 1998 using the MeSH 'myasthenia gravis' (restricted to the surgery subheading) and 'thymectomy'. The authors also reviewed the references of the identified articles.

Study selection
Study designs of evaluations included in the review
Controlled but non-randomised studies describing outcomes in MG patients with and without thymectomy were considered; some used historical controls.

Specific interventions included in the review
Thymectomy versus no thymectomy in patients with nonthymomatous autoimmune MG. Many studies did not describe the thymectomy technique employed; where it was described, transsternal and transcervical approaches were used.

Participants included in the review
Studies of patients with nonthymomatous autoimmune MG were included. Details of participants' gender, whether aged below 50 or 51 years (there was a discrepancy in the paper: in the text it was stated as patients younger than 50 years, whereas in the table it was stated as patients younger than 51 years), whether MG was severe (defined as Osserman grade 2B, 3 or 4) and whether MG was strictly ocular, were presented where primary studies had reported sufficient information. None of the studies described formal selection criteria for MG patients undergoing thymectomy.

MG patients undergoing thymectomy were younger, more often women and were more likely to have generalised and severe disease than those not undergoing thymectomy.

Outcomes assessed in the review
Medication-free remission (i.e. asymptomatic off medication), asymptomatic on or off medication, improvement since diagnosis and survival. Definitions of remission varied between studies and included: absence of MG signs or symptoms, mild restricted fixed residual weakness, ability to do a full day's work, and no signs or symptoms of MG for at least one year.

Follow-up, when described, varied from an average of 3 to 28 years.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. The following study characteristics were abstracted: method and setting of cohort assembly, years during which patients were enrolled in the cohort, number of patients assembled, duration of follow-up, proportion of patients lost to follow-up, the thymectomy techniques employed and MG outcomes (as described previously).

The following study population characteristics were also abstracted: proportion of patients younger than 50 or 51 years (discrepancy regarding age described previously) at the time of diagnosis of MG, the proportion of female patients, the proportion of patients with more severe MG at the time of diagnosis (defined by Osserman grade 2B, 3 or 4) and the proportion of patients with strictly ocular MG at the time of diagnosis.

The relative rate of thymectomy patients, compared with nonthymectomy patients attaining the outcomes, were calculated by dividing the thymectomy patient group's crude rate of achieving the outcome by that for the nonthymectomy patient group. The 95% confidence interval of these relative rates was also calculated.

In studies providing sufficient information, relative rates of outcomes after controlling for potential confounding variables of age, gender and severity of MG were calculated. Wilcoxon's test was used to determine the significance of the changes in relative rates measured after controlling for these variables.

Methods of synthesis
How were the studies combined?
The median relative outcome rates and mid-halftile of the controlled studies were calculated for each outcome as an estimate of the magnitude of benefit; these synthesised results were discussed narratively.

How were differences between studies investigated?
Differences between the studies were not statistically evaluated. There was a discussion of sources of heterogeneity in terms of surgical technique, length of follow-up, number of patients lost to follow-up, year of enrolment, patient characteristics such as severity and type of MG, data collection methods and definitions of remission.

The quality of three studies, whose results were not in the same direction as the others, were evaluated narratively to speculate the reasons for their conflicting results.

Results of the review
Twenty-eight non-randomised controlled studies describing outcomes in 21 MG cohorts were identified. Some articles described a subset of the cohort of other studies, therefore, it is not possible to calculate the total number of participants from the data presented. However, excluding those studies which may have duplicated patients from another cohort, the minimum total number of participants was 7,496.

With the exception of the cohorts described by 3 studies, the relative rates from individual studies indicated that MG patients undergoing thymectomy were more likely to achieve medication-free remission, become asymptomatic and improve, than MG patients not undergoing thymectomy. The association between thymectomy and improved outcomes achieved significance in 7 of the 15 studies describing medication-free remission, in 8 of the 12 studies describing asymptomatic patients on or off medication, in 8 of the 13 studies describing improvement, and in 4 of the 13 studies describing survival. No study described a significant negative association between thymectomy and any outcome. The median relative rates of outcomes in MG patients undergoing thymectomy were: for medication-free remission, 2.1 (mid-halftile: 1.4 - 2.7); for becoming asymptomatic, 1.6 (mid-halftile: 0.9 - 2.2), for improvement 1.7 (mid-halftile: 1.2 - 2.7) and for survival 1.1 (mid-halftile: 1.0 - 1.2).

The authors noted confounding differences in baseline characteristics of prognostic importance between thymectomy and nonthymectomy patient groups in all studies. In univariate analyses, persistent positive associations were seen between thymectomy and improved MG outcomes, whereas in multivariate analyses, there were conflicting associations between thymectomy and improved MG outcomes.

Authors' conclusions
The benefit of thymectomy in nonthymomatous autoimmune MG has not been established conclusively.

CRD commentary
The authors stated their review question clearly, although inclusion criteria were not clearly stated. It was unclear whether inclusion criteria for study design and participants were decided before or after the identification of studies.

The literature search was clearly described but was not thorough, and the authors did not report any attempt to identify unpublished or grey literature. This narrow search strategy may have missed relevant studies, allowing the introduction of selection bias. It was not stated whether language restrictions were applied. No analyses, e.g. a funnel plot, were conducted to assess publication bias.

Other electronic databases which may have been useful for identifying relevant literature include Science Citation Index, EMBASE, SIGLE, the National Research Register and the Cochrane Controlled Trials Register.

The validity of individual studies was not assessed. Confounding variables in the original studies were discussed in detail, and attempts to adjust for them included recalculating relative rates of outcomes within MG patient subgroups and controlling for confounding variables. The confounding effects noted by the authors may have been related to the non-randomised nature of patient allocation.

The authors do not report details relating to the process of decision making for study selection and data extraction, such as how many reviewers were involved, whether studies were examined independently, whether reviewers were blinded to source, and how disagreements were resolved.

Study details were reported in a table and supplemented by narrative discussion. However, they lacked detail relating to study design, participant characteristics, description of interventions, settings, outcome measures, efficacious results and side-effects. The authors stated that much of this data were not reported in the original studies.

Heterogeneity between studies was not statistically evaluated although there was a discussion of sources of heterogeneity, e.g. differences in intervention characteristics, outcome measurement, duration of follow-up and differences in findings, possibly accounted for by the wide range of years of publication. Pooling may have been inappropriate in light of these sources of heterogeneity.

Studies were not weighted for the analysis; there was no identification of the better quality studies. A forest plot was presented and the median value was calculated. Calculation of an estimate using a more representative statistic, such as the weighted mean, would have been more justified.

Owing to the limitations stated above in relation to review methodology, selection bias, heterogeneity of studies and the confounding variables discussed by the authors, the authors' conclusion that the benefit of thymectomy has not been established conclusively is concurred.

Implications of the review for practice and research
Practice: The authors state that for patients with nonthymomatous autoimmune MG, thymectomy is recommended as an option to increase the probability of remission or improvement.

Research: The authors state that all currently published studies have serious methodological flaws that prevent definitive conclusions regarding the benefit of thymectomy. In view of these serious limitations, a well-designed controlled trial is essential. If a well-designed, prospective, controlled study demonstrates that thymectomy is beneficial, then future studies could address the timing of thymectomy, which patients benefit most and the role of other therapies in relation to thymectomy.

Bibliographic details
Indexing Status
Subject indexing assigned by NLM

MeSH
Cohort Studies; Humans; Myasthenia Gravis /surgery; Prognosis; Thymectomy

AccessionNumber
12000001424

Date bibliographic record published
31/01/2002

Date abstract record published
31/01/2002

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.