Treatement modalities for Graves' ophthalmopathy: systematic review and metaanalysis
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CRD summary
The authors concluded that intravenous corticosteroids were effective for decreasing the clinical activity score in patients with moderate to severe Graves' ophthalmopathy; other treatment comparisons were less clear. The use of multiple outcome measures together with small sample sizes and a large number of studies of uncertain quality represented limitations and the conclusions should be interpreted with caution.

Authors' objectives
To compare treatment modalities for Graves' ophthalmopathy versus placebo, no treatment or other interventions.

Searching
PubMed and The Cochrane Library were searched with no publication or language restrictions to June 2008. Search terms were reported and included a search filter for randomised controlled trials. Reference lists of included studies and reviews were screened for additional studies.

Study selection
Randomised controlled trials (RCTs) that compared treatment modalities for Graves' ophthalmopathy versus placebo, no intervention or other treatments were eligible for inclusion. Studies where ophthalmopathy was a secondary outcome from treatment or studies that evaluated treatments for alleviating selected complications of Graves' ophthalmopathy, including diplopia or exophthalmos, were excluded. Comparisons varied by treatment and dose, but were grouped as: oral corticosteroids versus intravenous corticosteroids; somatostatin analogues versus placebo; orbital radiotherapy versus control; orbital radiotherapy plus corticosteroids versus radiation or corticosteroids alone; high- versus low-dose radiation; and other comparisons (therapeutic interventions versus placebo or control and head-to-head comparisons).
The primary outcome was the clinical activity score (CAS). Ophthalmology index or total eye score was used in studies prior to the introduction of CAS. Secondary outcomes included: NOSPECS scheme; diplopia; proptosis; optic neuropathy in either eye; subjective outcome measures; visual acuity; local eye irritation; and adverse events. In the included studies, mean or median age ranged from 36.1 to 64.1 years. Patients had moderately severe to severe Graves' ophthalmopathy or moderate Graves' ophthalmopathy in most studies.

Two reviewers independently selected studies for inclusion in the review.

Assessment of study quality
Two reviewers independently assessed study quality using the criteria: allocation concealment; generation of allocation sequence; and blinding. Allocation concealment and generation of allocation sequence were graded as adequate, unclear or inadequate. Type of analysis (per protocol or intention to treat) was assessed.

Data extraction
Data for dichotomous outcomes were extracted to calculate odds ratios (OR). Means and standard deviations were extracted for continuous outcomes. Authors were contacted for missing data where necessary.

Two reviewers independently extracted data for the review; disagreements were resolved by a third reviewer extracting data.

Methods of synthesis
Modified intention-to-treat data were pooled using a fixed-effect model. Dichotomous data were combined to calculate pooled odds ratios and continuous data combined to calculate mean difference or standardised mean differences (SMDs), both with 95% CIs. A random-effects model was used if significant heterogeneity was present. Heterogeneity was assessed using $\chi^2$ and $I^2$. Tests with significant heterogeneity were defined as $p<0.10$ or $I^2>50%$. Sensitivity
analysis was carried out to assess the effect of the quality of allocation concealment, allocation generation and blinding.

**Results of the review**

A total of 33 RCTs were included in the review (n=1,367, range 14 to 97). For study quality: allocation concealment was adequate in 15 studies, unclear in 15 studies and inadequate in three studies; and generation of allocation sequence was adequate in 15 studies, unclear in 16 studies and inadequate in two studies. Duration of follow-up ranged from eight weeks to three years.

For patients with moderate to severe Graves' ophthalmopathy, CAS was significantly reduced by intravenous pulse corticosteroids compared to oral corticosteroids (SMD -0.64, 95% CI -1.11 to -0.17; four studies). There were significantly more adverse events in the intravenous group (OR 0.12, 95% CI 0.05 to 0.26). Heterogeneity was present (p=0.05).

Compared with placebo, somatostatin analogues exhibited a significant improvement in CAS compared to placebo (mean difference -0.63, 95% CI -0.98 to -0.28; four studies). Significant heterogeneity was absent.

Compared with control, radiotherapy was superior for response rates of diplopia (OR 4.88, 95% CI 1.93 to 12.34; two studies).

Treatment with a combination of orbital radiotherapy and corticosteroids was significantly improved compared to treatment alone (SMD -1.05, 95% CI -1.62 to -0.48; one study) and the addition of radiotherapy to corticosteroids was superior to corticosteroids alone (SMD -1.4, 95% CI -2.3 to -0.65; two studies); significant heterogeneity was present for these comparisons.

**Authors' conclusions**

Current evidence demonstrated the efficacy of intravenous corticosteroids in decreasing CAS in patients with moderate to severe Graves' ophthalmopathy. Intravenous pulse corticosteroids therapy had a small but statistically significant advantage over oral therapy and caused significantly fewer adverse events. Somatostatin analogues had marginal clinical efficacy. The efficacy of orbital radiotherapy as single therapy remained unclear. The combination of radiotherapy with corticosteroids had better efficacy than either radiotherapy or oral corticosteroids alone.

**CRD commentary**

The review question and inclusion criteria were clear. A limited search of databases was undertaken; no language or publication status restrictions were placed upon the search, which reduced potential for language and publication biases. All stages of the review process were conducted in duplicate, which reduced potential for error and bias. Appropriate criteria were used to assess the quality of the included studies; most included studies were small and around half of the included studies did not clearly report quality criteria, so the quality of the evidence-base was uncertain for a number of studies. Suitable methods were undertaken to assess statistical heterogeneity. Generally this is a well-conducted review, but as acknowledged by the authors the use of multiple outcome measures, often without a primary outcome, together with small sample sizes and a large number of studies of uncertain quality represented limitations to the review and the conclusions should be interpreted with caution.

**Implications of the review for practice and research**

**Practice:** The authors did not state any implications for practice.

**Research:** The authors stated that further research was required to assess what factors exacerbated ophthalmopathy and how to prevent its appearance, as well as the optimal management of patients with optic neuropathy and mild active Graves' ophthalmopathy.

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