The use of corticosteroids versus other treatments for Graves' ophthalmopathy: a quantitative evaluation

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CRD summary
This review assessed the use of corticosteroids in the treatment of Graves' ophthalmopathy. The authors concluded that oral corticosteroids administered in combination with radiotherapy, and intravenous corticosteroids with or without radiotherapy, were the most effective treatments. Given the lack of a quality assessment, and the pooling of different outcome measures and study designs, the conclusions should be viewed cautiously.

Authors' objectives
To assess the efficacy of corticosteroids, compared with other treatments, for the treatment of Graves' ophthalmopathy.

Searching
MEDLINE was searched from 1966 to 2001; the search terms were reported. An Internet search of conference abstracts and a manual search of the references of retrieved articles were also performed.

Study selection

Study designs of evaluations included in the review
The inclusion criteria specified experimental or observational studies, although the authors stated elsewhere that inclusion was restricted to cohort studies and randomised trials.

Specific interventions included in the review
The inclusion criteria did not specify the eligible interventions. The actual interventions included were: corticosteroids alone compared with no treatment or any other treatment; oral corticosteroids plus radiotherapy compared with oral corticosteroids or radiotherapy alone; and intravenous (IV) corticosteroids, with or without radiotherapy, compared with oral corticosteroids and/or radiotherapy. One study assessed prednisone; details of the corticosteroids used in other studies were not provided. The doses of oral treatment ranged from 1 mg/kg to 100 mg. The duration of treatment ranged from 6 weeks (IV) to 9 months (oral), with an average of 5 to 6 months.

Participants included in the review
No details of the participants included in the review were provided, either in the inclusion criteria or the study details.

Outcomes assessed in the review
The inclusion criteria specified that studies needed to have clear criteria for assessing whether the outcome after treatment was successful or not. Studies were eligible for inclusion if the relative failure rate could be calculated. The actual outcome used in the review was ‘risk of failure’, a dichotomous outcome categorised as ‘getting worse or no change’ and ‘better’. The criteria used to assess this outcome differed between the studies and included: Donaldson's Clinical Criteria; a subjective questionnaire; 4 objective criteria where meeting 3 out of 4 was a response; the NOSPECS symptom classification system; and a symptom severity score. Further details of how the outcomes were measured using these criteria were not provided.

How were decisions on the relevance of primary studies made?
The authors stated that they examined potentially eligible studies independently, but did not state how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.
Data extraction
The authors did not state how the data were extracted for review, or how many reviewers performed the data extraction. Data on the number of patients 'better' or 'same or worse' in each treatment and control group were extracted. The relative risk (RR) for each study was calculated as the risk of treatment failure for the corticosteroid treatment group divided by the risk of treatment failure for the control group.

Methods of synthesis
How were the studies combined?
The studies were analysed as three separate groups: the assessment of corticosteroids alone versus no treatment or any other treatment (7 studies); the assessment of oral corticosteroids plus radiotherapy versus either treatment alone (5 studies); and the assessment of IV corticosteroids, with or without radiotherapy, versus oral corticosteroids and/or radiotherapy (3 studies). One cohort study contributed to both the oral and IV groups. The authors then went on to pool the oral/radiotherapy and the IV groups of studies.

Studies were combined using both fixed-effect and random-effects meta-analyses. Publication bias was assessed using Egger's regression analysis. Subgroup analyses were performed to investigate the effect of sample size (less than or greater than 50 participants), risk of failure in the control group (less than or greater than 22%), year of publication (before or after 1990) and study design.

How were differences between studies investigated?
Differences between the studies were assessed using Cochran’s Q test.

Results of the review
Fourteen studies were included: 9 randomised trials (406 participants) and 5 cohort studies (393 participants).

The studies assessing corticosteroids alone were not pooled, owing to statistical heterogeneity, and no further analysis of these studies was undertaken.

No evidence of statistical heterogeneity was found between the studies assessing oral corticosteroids and radiotherapy (Q test, P=0.59), or between the studies assessing IV corticosteroids (Q test, P=0.98). Treatment with oral corticosteroids plus radiotherapy was associated with a statistically significant reduction in the number of treatment failures (RR 0.3, 95% confidence interval, CI: 0.15, 0.6), compared with treatment with oral corticosteroids or radiotherapy alone. Treatment with IV corticosteroids, with or without radiotherapy, was also associated with a statistically significant reduction in the number of treatment failures (RR 0.36, 95% CI: 0.19, 0.66). The results from the random-effects analyses were similar.

When the 7 oral corticosteroids plus radiotherapy studies were pooled with the 3 IV corticosteroid studies, the overall RR was 0.3 (CI not reported). From this, the number of patients who needed to be treated with oral corticosteroids plus radiotherapy, or IV corticosteroids, to prevent one more failure in comparison with other treatments was estimated to be between three and eight. The results were similar across subgroups by sample size, publication year, study design and risk of failure in the control group (these results were not presented). A regression analysis investigating publication bias suggested that some publication bias may have been present.

Authors' conclusions
Treatment with oral corticosteroids plus radiotherapy, or IV corticosteroids with or without radiotherapy, is more efficient in treating Graves' ophthalmopathy than other conventional treatments.

CRD commentary
The inclusion criteria for this review were not defined clearly. The search was restricted to one database, conference abstracts and reference lists. In addition, only English language studies were included, which may have introduced bias. It was unclear how decisions about the eligibility of studies were made. No quality assessment was undertaken, thus it
was not possible to judge the potential for bias in those studies that were included. No information on the study participants or the control group interventions were presented. The outcomes were measured using various criteria, but there were no details of how treatment failure was defined in the individual studies.

Differences between the studies were assessed statistically, but different study designs were pooled in the meta-analyses without regard for the potential for bias and confounding in the observational studies. The results of the pooled analyses are unlikely to be reliable. Hence, the authors’ conclusions should be viewed cautiously.

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

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

**Research:** The authors made recommendations for further research. Future research should investigate: the role of IV corticosteroids alone compared with IV corticosteroids combined with oral corticosteroids or radiotherapy; the most effective dose of IV corticosteroids; the safety of IV corticosteroids; the relapse rate after IV treatment and whether oral treatment is needed for a sustained effect; and which aspects of Graves’ ophthalmopathy can be treated by IV corticosteroids.

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