Meta-analysis of methylprednisolone pulse therapy for Graves' ophthalmopathy
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CRD summary
The review concluded that intravenous glucocorticoid therapy (steroids injected into the bloodstream) were more efficient in treating people with active and moderate-to-severe Graves' ophthalmopathy (eye disease linked with thyroid disease); this therapy was better tolerated than glucocorticoids taken by mouth. Several review limitations make it difficult to fully evaluate the reliability and clinical significance of these conclusions.

Authors' objectives
To evaluate the efficacy of glucocorticoids for treating Graves' ophthalmopathy.

Searching
PubMed, EMBASE, Chinese Biomedicine Database and The Cochrane Library were searched for published studies from 1969 up to December 2012. Reference lists of retrieved studies were also searched.

Study selection
Randomised controlled trials (RCTs) that assessed the effect of intravenous glucocorticoids compared with oral glucocorticoids, orbital radiotherapy, orbital decompression or placebo in patients with active and moderate-to-severe Graves' ophthalmopathy were eligible for inclusion. Trials had to report treatment success rate (example outcomes were stated), clinical activity score, or absolute reduction in proptosis (forward displacement of the eye) at the end of follow up.

Most of the included trials compared intravenous with oral glucocorticoids. Most included patients had not received any prior treatment. The authors stated that methylprednisolone doses ranged from 4.5g to 12g (but no further details for individual trials were provided). Treatment durations ranged from three to 13 months. Three-quarters of patients were female and most had moderate-to-severe disease (patients had severe disease in one trial). Mean ages ranged from 32 to 56 years. The trials were all single-centre studies performed in either Italy, The Netherlands, Germany, Turkey or China. Trials were published between 2001 and 2008.

Two reviewers independently selected studies for inclusion.

Assessment of study quality
Two reviewers assessed trial quality using the following scoring system: allocation concealment, adequate (1 point), inadequate or unclear (0 points); blinding, double-blind (2 points), single-blind (1 point), and open label (0 points); intention-to-treat analysis, used (1 point), not used or unable to assess (0 points); and losses to follow-up, given (1 point), and not given (0 points).

Data extraction
Intention-to-treat data were extracted to calculate risk ratios or mean differences with 95% confidence intervals. Two reviewers independently extracted data, with disagreements resolved by discussion.

Methods of synthesis
Meta-analyses were performed to calculate pooled risk ratios or weighted mean differences using a random-effects model. Heterogeneity was assessed using $I^2$ (with $I^2$=50% to 75% indicating moderate heterogeneity and $I^2$=75% to 100% extreme heterogeneity).

Results of the review
Eight RCTs were included in the review (376 patients). Allocation concealment methods were adequate in six trials and unclear in two. Participants were blinded in one trial, examiners were blinded in five trials, but none of the trials blinded trial investigators. Withdrawals rates ranged from 0 to 7%. The mean quality score was 3.1.

Intravenous glucocorticoids showed statistically significantly higher effective rates compared with placebo (RR 7.5,
95% CI 1.1 to 49.3; one RCT) and oral glucocorticoids (RR 1.48, 95% CI 1.18 to 1.86; three RCTs; I²=0%). Intravenous glucocorticoids also significantly reduced clinical activity score compared with oral glucocorticoids (WMD 0.86, 95% CI 0.53 to 1.18; three RCTs; I²=0%).

The combination of intravenous glucocorticoids and orbital radiotherapy resulted in significantly higher effective rates (RR 1.40, 95% CI 1.11 to 1.77; two RCTs; I²=0%) than combined oral glucocorticoids and orbital radiotherapy. Combined intravenous glucocorticoids and orbital radiotherapy significantly also reduced clinical activity score (WMD 0.66, 95% CI 0.30 to 1.02; two RCTs; I²=0%). Five trials reported on proptosis with no significant differences found between any treatments.

For adverse effects, statistically significantly higher rates were found in the oral group when compared with the intravenous group for Cushingoid features (RR 0.21, 95% CI 0.12 to 0.38; three RCTs) and weight gain (RR 0.21, 95% CI 0.06 to 0.68; two RCTs) but not for palpitations, myalgia, hypertension, sleepiness, depression, gastrointestinal effects, and hyperglycaemia.

Authors' conclusions
Intravenous glucocorticoid therapy was associated with significantly greater efficacy in the treatment of patients with active and moderate-to-severe Graves' ophthalmopathy and was better tolerated than oral glucocorticoids.

CRD commentary
The review addressed a clear question and was supported by reproducible eligibility criteria. However, the authors did not fully adhere to their review eligibility criteria, as one trial (which caused significant heterogeneity in their meta-analyses) was excluded from the review purely for showing different results from the other included trials.

Efforts to identify trials were undertaken by searching several databases, but it was unclear whether there were any language restrictions, and only published studies were sought. Therefore, it was possible that some relevant trials may have been missed. However, suitable methods (such as independent duplicate processes) were used to reduce the risk of reviewer error and bias throughout the review.

Appropriate methods were used to pool data and to assess heterogeneity. Although a quality assessment was performed, the results were used little when interpreting the validity of the meta-analysis results. For individual trials neither the specific glucocorticoids and doses, nor the specific outcomes on which success rate calculations were based, were reported. The clinical significance of the clinical activity score reductions reported were also not evaluated. These factors made it difficult to interpret the review results.

Although the authors' conclusions appear reasonable based on the included trials, review limitations make it difficult to fully evaluate their reliability and clinical significance.

Implications of the review for practice and research
Practice: The authors proposed that intravenous glucocorticoids should be the primary choice for treatment of Graves' ophthalmopathy since it was as efficient as oral treatment and produced fewer side effects, so more easily accepted by patients. They added that limiting the total cumulative dose of methylprednisolone and measuring liver enzymes during treatment were indispensable.

Research: The authors stated that other potential strategies to reduce the risk of relapse/progression of Graves' ophthalmopathy at the end of intravenous glucocorticoid therapy needed to be explored.

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