Intravitreal triamcinolone acetonide injection for treatment of refractory diabetic macular edema: a systematic review


CRD summary
This review concluded that intravitreal triamcinolone acetonide injection was effective in improving visual acuity in patients with refractory diabetic macular oedema in the short-term. This was generally a well-conducted review and the authors’ conclusions appear to reflect the evidence. However, limitations within the included trials should be taken into account when interpreting the conclusion.

Authors’ objectives
To compare intravitreal triamcinolone acetonide injection versus no treatment or sub-Tenon triamcinolone acetonide (STTA) injection in improving visual acuity of patients with refractory diabetic macular oedema.

Searching
MEDLINE, the Cochrane Library, TRIP, ClinicalTrials.gov and Google Scholar were searched without language, or other restrictions, to September 2008. Search terms were reported. Abstracts of the Association for Research in Vision and Ophthalmology were also searched from 2005 onwards. Reference lists of included studies were scanned and experts were consulted for additional studies.

Study selection
Randomized controlled trials (RCTs) that compared intravitreal triamcinolone acetonide injection with no treatment or STTA injection were eligible for inclusion. Trials including patients with refractory diabetic macular oedema, unresponsive to focal laser treatment and those that assessed visual acuity following at least three months follow-up were also eligible. The primary outcome was visual acuity. Additional outcomes included central macular thickness and intraocular pressure.

In included trials the triamcinolone acetonide formulation included: Kenacort, Triamcinolona, Ophalmos Lab, Kenalog, Lidocaine and saline; intravitreal triamcinolone acetonide was mostly administered at doses of 4mg. The age of patients in the included trials ranged from 59 to 67 years and the proportion of males ranged from 42.6 to 55.7% (where stated). Diabetic macular oedema duration prior to trial recruitment varied.

Two reviewers independently selected studies for inclusion in the review, with disagreements resolved by consensus.

Assessment of study quality
Two reviewers independently assessed the methodological quality of the included trials by using the Jadad scale, a 5 point scale evaluating randomisation, blinding, withdrawals and drop-outs. Trials were considered high quality if they scored at least 3 points. Disagreements were resolved by consensus.

Data extraction
Two reviewers independently extracted data for pre-defined continuous outcomes using a standardised data extraction form. Disagreements were resolved by consensus.

Methods of synthesis
The pooled weighted mean difference (WMD) and corresponding 95% confidence intervals (CI) were calculated using a fixed-effect model. Statistical heterogeneity was assessed using the $\chi^2$ and $I^2$ statistics; trials with significant heterogeneity were removed from the analysis. Subgroup analyses were conducted for comparisons, intravitreal triamcinolone acetonide injection was compared with placebo or no treatment or to STTA injection. Sensitivity analysis was undertaken using trial quality. Publication bias was assessed using funnel plots.

Results of the review
Six RCTs were included in the review (n=207 patients, range 12 to 61); four studies were considered to be of high quality. Duration of follow-up ranged from four to 24 months, but for most studies was six months or less. Funnel plots indicated the presence of publication bias.

**Visual acuity**: Compared with placebo or no treatment, intravitreal triamcinolone acetonide injection yielded significantly greater improvement in visual acuity (measured in logarithm of the minimum angle of resolution units) at three months (WMD -0.10, 95% CI -0.20 to 0.00; four trials) but did not differ significantly at six months (WMD -0.05, 95% CI -0.15 to 0.05; four trials). Compared with sub-Tenon triamcinolone acetonide (STTA) injection, intravitreal triamcinolone acetonide injection demonstrated significantly greater improvement in visual acuity at three months (WMD -0.09, 95% CI -0.16 to -0.01; two trials) but not at six months (WMD -0.02, 95% CI -0.10 to 0.05; two trials).

**Central macular thickness**: Compared with placebo or no treatment, intravitreal triamcinolone acetonide injection yielded significantly greater reduction in central macular thickness at three months (WMD -130.59 μm, 95% CI -161.45 to -99.73; four trials) and at six months (WMD -53.08 μm, 95% CI -104.16 to -2.02; four trials). Compared with STTA injection, intravitreal triamcinolone acetonide injection demonstrated significantly greater reduction in central macular thickness at three months (WMD -120.77 μm, 95% CI -167.25 to -74.29; two trials) but not at six months. Significant heterogeneity was present for the comparison of intravitreal triamcinolone acetonide injection with placebo at three months ($I^2$=74.7%). There was a discrepancy between the forest plots and texts for this comparison.

**Intraocular pressure**: Compared with placebo or no treatment, patients receiving intravitreal triamcinolone acetonide injection had significantly higher intraocular pressure at three months (WMD 4.33mmHg, 95% CI 2.88 to 5.77; four trials; there was a discrepancy between the forest plots and texts for this comparison) and at six months (WMD 2.40mmHg, 95% CI 1.37 to 3.44; four trials). Intravitreal triamcinolone acetonide injection demonstrated no difference in intraocular pressure at three months or six months.

The sensitivity analysis (three trials) found no significant difference in visual acuity at three months.

**Authors’ conclusions**
Intravitreal triamcinolone acetonide injection was effective in improving visual acuity in patients with refractory diabetic macular oedema in the short-term, but the benefits did not seem to persist in the long-term.

**CRD commentary**
The review question and inclusion criteria were clear. Few details were reported for patient characteristics, so it was unclear whether patients were comparable at baseline. The search included a number of appropriate databases and was designed to minimise language bias. Publication bias was assessed and found to be present. Steps were taken to minimise reviewer bias and errors in all parts of the review process. Appropriate criteria were used to assess the quality of the included trials; three trials scored 3 points or less, suggesting that half of the trials were not of the highest quality. All included trials had small sample sizes. Standard statistical methods were used to pool the data. Potential sources of heterogeneity were appropriately explored and were absent from the majority of (but not all) comparisons. This was generally a well-conducted review. The authors’ conclusions appeared to reflect the evidence presented. Limitations of the included trials, acknowledged by the authors, regarding trial quality, small trial sizes and the presence of publication bias, should be borne in mind when interpreting the results.

**Implications of the review for practice and research**
**Practice**: The authors stated that focal/grid laser photocoagulation should be considered the first-line therapeutic option for patients with diabetic macular oedema. The decision to undergo intravitreal triamcinolone acetonide treatment should reflect the patient's personal preferences, in light of the risks and benefits of potential treatment. Intravitreal triamcinolone acetonide treatment should be reserved for certain selected cases.

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