Quantifying the effect of intraocular pressure reduction on the occurrence of glaucoma

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CRD summary
The authors' conclusion that topical hypotensive therapy reduced the risk of conversion to glaucoma in ocular hypotension patients reflected the evidence presented and is likely to be reliable; however, the conclusion that the risk of conversion to glaucoma decreased by approximately 14% for each mmHg of intra-ocular pressure reduction (meta-regression result) should be interpreted with more caution.

Authors' objectives
To determine the effect of reducing intra-ocular pressure on the incidence of primary open-angle glaucoma and the progression of glaucoma in patients with ocular hypertension.

Searching
MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched up to November 2007; search terms were reported. Reference lists of relevant articles were checked. Publications in English, French, German, or Dutch were eligible.

Study selection
Randomised controlled trials (RCTs) that compared intra-ocular pressure reduction intervention with placebo or no treatment in patients with ocular hypertension or primary open-angle glaucoma, reporting visual field loss or optic disc changes, were eligible for inclusion. Eligible trials were required to have follow-up of greater than six months.

In included trials, intra-ocular pressure lowering interventions included: dorzolamide (2% injected dose), betaxolol (twice daily), timolol (0.25% to 0.5% twice daily), topical epinephrine (2% bid), epinephrine hydrochloride (1% to 2% bid) and topical medication (test point ≤24 or less and >20% reduction). Most trials included patients with ocular hypertension; one trial included participants with primary open-angle glaucoma. Mean follow-up for ocular hypertension trials ranged from 37.5 to 72 months (where reported).

Two reviewers independently selected trials for inclusion in the review; the authors did not state how disagreements were resolved.

Assessment of study quality
Two reviewers independently assessed the quality of the included trials using a 16-item check list. Criteria assessed included: concealment of randomisation procedure; description of interventions, outcome assessment, and side effects; blinding; comparability in baseline prognostic indicators, interventions, and follow-up between groups; intention-to-treat; sample size calculation; and inclusion of point estimates for primary outcomes; resulting in a total score between 0 and 16. Any disagreements were resolved through discussion.

Data extraction
Data were extracted to permit the calculation of relative risks (RRs) and their associated 95% confidence intervals (CIs) for the cumulative incidence of glaucoma. Patients lost to follow-up were assumed to have the same probability of developing glaucoma as the group without treatment. Patients reaching a safety endpoint for intra-ocular pressure were considered to have developed glaucoma.

It appeared that two reviewers independently extracted data from the primary trials.

Methods of synthesis
Trials were combined in a meta-analysis using a random-effects model. Summary estimates were reported as relative risks with 95% confidence intervals. Statistical heterogeneity was assessed by observation of the forest plot, and by the Q-test and $I^2$ statistic. Meta-regression was also used to determine the glaucoma risk reduction (per mmHg) of intra-ocular pressure reduction.
ocular pressure reduction achieved through therapy.

Sensitivity analyses were performed to investigate: the robustness of findings to different assumptions (fixed-effect versus random-effects models); the exclusion of poorer quality trials (quality score of less than 10); the addition of a hypothetical trial with no treatment effect; and different relative risk values (calculations for these values were reported) for one trial where a significant loss to follow-up was observed; when patients who reached a safety point (intra-ocular pressure >35mmHg) were excluded from the trial.

Publication bias was assessed using Egger's test.

Results of the review
Ten trials were included in the review (n=not reported). Nine trials included patients with ocular hypertension; one trial included patients with primary open-angle glaucoma. Quality scores ranged from 6 to 14; five ocular hypertension trials had a quality score above 10. The nine ocular hypertension trials were included in the meta-analysis (n=3,673 patients).

A significant reduction in the rate of glaucoma was found with intra-ocular pressure lowering interventions in patients with ocular hypertension compared with control groups (RR 0.61, 95% CI 0.45 to 0.83; I²=47%). No evidence of publication bias was found and sensitivity analyses did not significantly alter the findings.

Meta-regression analysis suggested that the relative risks of conversion to glaucoma decreased with an increase in difference in the achieved intra-ocular pressure reduction between the control and the intervention group, i.e. with each mmHg of intra-ocular pressure reduction after therapy, the risk of conversion to glaucoma decreased by approximately 14%.

Authors' conclusions
Topical hypotensive therapy reduced the risk of conversion to glaucoma in ocular hypertension, and that the risk of conversion to glaucoma in patients with ocular hypertension decreased by approximately 14% for each mmHg of extra intra-ocular pressure reduction.

CRD commentary
The review question was supported by clear inclusion criteria. Several databases were searched, but the decision to limit the review to studies reported in four specific languages may have led to the omission of some relevant trials. No specific attempts were made to locate unpublished trials, which raised the possibility of publication bias; no evidence of publication bias was found when assessed, but the small number of trials involved made this assessment difficult to interpret. Methods designed to reduce the likelihood of reviewer bias and error were reported for each stage in the review process.

A formal assessment of trial quality was performed; both summary and individual results were reported. Pooling of data appeared appropriate. Statistical heterogeneity was assessed. Sensitivity analyses were performed.

The authors’ conclusion that ocular hypotension therapy reduced the risk of conversion to glaucoma reflected the evidence presented and is likely to be reliable. However, results from the meta-regression should be interpreted with more caution, as meta-regression does not prove causality and should be regarded as hypothesis generating.

Implications of the review for practice and research
Practice: The authors do not state any implications for practice.

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