The intraocular pressure-lowering effect of prostaglandin analogs combined with topical beta-blocker therapy: a systematic review and meta-analysis

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CRD summary
The aim was to estimate the intraocular pressure-lowering effect of prostaglandin analogues added to topical beta-blocker therapy in patients with primary open-angle glaucoma or ocular hypertension. Latanoprost added to timolol reduced intraocular pressure more than switching to a fixed combination. The reliability of the conclusion is unclear due to limitations in the review process and reporting.

Authors' objectives
To estimate the intraocular pressure-lowering effect of prostaglandin analogues, when added to topical beta-blocker therapy, in patients with primary open-angle glaucoma or ocular hypertension.

Searching
MEDLINE, EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for studies in English, French, German, or Dutch included between 1990 and August 2009. Search terms were not reported, but references were given for related reviews (for the most recent reference, see Other Publications of Related Interest).

Study selection
Randomised trials studying the combination of topical beta-blocker therapy with bimatoprost, latanoprost, or travoprost were eligible. Trials had to report absolute and relative change in intraocular pressure after a follow-up of at least one month and no more than three months. Trials of patients with secondary and congenital glaucoma, and trials where less than 85% of patients had primary open-angle glaucoma or ocular hypertension, were excluded.

In most trials treatment was administered either as a concomitant or fixed combination after a run-in period on beta-blocker therapy, or after a washout period. Where reported, timolol (0.5%) was the beta-blocker, most commonly given with latanoprost (0.005%). Some trials were placebo-controlled. The mean age of patients ranged from 59 to 71 years.

The authors did not state how many reviewers selected trials.

Assessment of study quality
The Delphi list, with additional items added, was used to evaluate trial quality. Trials were given a score with one point for a 'yes' response to an item, and no points for a 'no', 'don't know', or 'uncertain' response. The maximum possible score was 20. The authors did not state how many reviewers performed the quality assessment.

Data extraction
The mean, highest decrease, and lowest decrease, diurnal intraocular pressure measurements were extracted with standard errors. Peak and trough moments as advised by the American Academy of Ophthalmology were used when the change at only one time point was reported. The results from the time points closest to one month were used. For crossover trials, the data were extracted only for the period before the crossover. The authors did not state how many reviewers extracted data.

Methods of synthesis
Meta-analyses were performed to calculate pooled absolute or relative mean differences in intraocular pressure with 95% confidence intervals. The authors reported that a random-effects model was used because there was heterogeneity between trials, but no assessment of heterogeneity was reported.

Results of the review
Twenty-nine trials, with 36 groups (33 treatment and three control), were included. The mean quality score was 14.6 (range 11 to 18). The percentage of withdrawals ranged from zero to 25.7. Allocation concealment was reported in seven trials. The mean follow-up period was 7.3 weeks (range four to 13 weeks). The frequency and duration of
measurements after drug administration varied across trials.

Adding latanoprost in the evening to timolol twice-daily reduced pressure by 6.3mmHg (95% CI 5.5 to 7.1; three trials). Switching from timolol twice daily to a once-daily fixed combination of timolol and latanoprost in the morning reduced pressure by 2.8mmHg (95% CI 2.3 to 3.3; four trials).

After complete washout, starting with any fixed combination of timolol and a prostaglandin analogue in the morning reduced pressure by 8.4mmHg (95% CI 7.6 to 9.1; five trials), with the pooled highest decrease being 9.1mmHg (95% CI 8.2 to 9.9; seven trials) and the lowest decrease 7.9mmHg (95% CI 7.2 to 8.5; eight trials).

After complete washout, starting with any fixed combination of timolol and a prostaglandin analogue in the evening reduce pressure by 8.6mmHg (95% CI 8.0 to 9.2; five trials), with the pooled highest decrease being 10.1mmHg (95% CI 9.2 to 11.0; five trials) and the lowest decrease 7.3mmHg (95% CI 6.4 to 8.1; five trials). Further results were reported.

**Authors' conclusions**
The addition of latanoprost to timolol reduced intraocular pressure more than switching to the fixed combination. There was no difference between evening and morning dosing. Greater reductions after evening dosing were explained by differences in trial design.

**CRD commentary**
The review addressed a clear question and was supported by appropriate eligibility criteria. Attempts to identify trials were undertaken by searching electronic databases. There were some attempts to minimise the risk of language bias, but the possibility of publication bias remained (there was no specific search for unpublished trials). It was unclear whether the authors made sufficient attempts to minimise errors and biases in the review process (by using independent duplicate processes). Trial quality was assessed, but the results were not used when interpreting the results of the review. Sufficient trial details were provided and appropriate methods appear to have been used to pool the data. Heterogeneity was not assessed, but the authors tried to minimise heterogeneity by using strict eligibility criteria.

The reliability of the authors’ conclusions is unclear due to limitations in the review process and reporting.

**Implications of the review for practice and research**
The authors did not state any implications for research and practice.

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