A meta-analysis of topical prostaglandin analogues intra-ocular pressure lowering in glaucoma therapy

Denis Ph, Lafuma A, Khoshnood B, Minaud V, Berdeaux G

CRD summary
This review reported that, for patients with open angle glaucoma or ocular hypertension, travoprost and bimatoprost may be more effective than latanoprost for lowering intraocular pressure. However, limitations in both the analysis and methods of the review suggest that the findings may not be reliable.

Authors’ objectives
To compare the efficacy of different topical prostaglandin analogues for the treatment of glaucoma.

Searching
MEDLINE and EMBASE were searched for studies published in French or English between 2001 and 2004; the search terms were reported. Unpublished studies were excluded from the review.

Study selection
Study designs of evaluations included in the review
RCTs were eligible for inclusion. Crossover trials were excluded.

Specific interventions included in the review
Studies comparing at least two of three topical prostaglandin analogues (latanoprost, bimatoprost and travoprost) used as monotherapies were eligible for inclusion. The drug dosages were not reported, but one study was excluded because it did not use dosages in accordance with the ‘Summary of Product Characteristics’. The majority of included participants were treated with latanoprost, with similar numbers receiving either travoprost or bimatoprost. Latanoprost was compared with travoprost (2 randomised controlled trials, RCTs), bimatoprost (3 RCTs), and travoprost and bimatoprost (2 RCTs). Two RCTs compared travoprost with bimatoprost.

Participants included in the review
Studies of patients with a diagnosis of open angle glaucoma or ocular hypertension were eligible for inclusion. The mean age of the included participants ranged from 56.7 to 68.8 years and, where stated, 57.3% were female and 67.2% were Caucasian. The majority of the participants suffered from open angle glaucoma (69.7%); 28.7% suffered from ocular hypertension and 0.9% from another type of glaucoma. The baseline intraocular pressure (IOP) ranged from 22.3 to 26.5 mmHg.

Outcomes assessed in the review
The primary outcome was the IOP, which had to be measured at baseline and follow-up. The predicted number of patients who responded favourably to treatment was also assessed; a favourable response was defined as an IOP of less than 18 mmHg. In the included studies, outcomes were followed up over a mean period of 4.3 months (range: 0.5 to 12).

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or 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 the review, or how many reviewers performed the data extraction. Mean IOP values with standard deviations (SDs) were calculated from intention-to-treat data. The daily average IOP was calculated where several measurements were available over the time period, otherwise the IOP at the
end of the follow-up period was used. Where SDs were not reported, they were calculated from the number of patients and the standard error of the mean, or from the sample size-weighted SD from other studies. The number of patients who responded favourably to treatment was estimated using the mean IOP values and the corresponding SD, assuming a normal distribution for IOP.

**Methods of synthesis**

How were the studies combined?
The studies were grouped according to treatment with latanoprost used as the reference treatment. Pooled mean IOPs together with 95% confidence intervals (CIs) were calculated using a random-effects model. Poisson regression models were used to calculate the pooled incident rate of responders (IRRs) with 95% CIs. Publication bias was assessed using the Begg and Mazumdar adjusted rank correlation test and the Egger regression asymmetry test.

How were differences between studies investigated?
Clinical differences and similarities were evident from the data tables and some were discussed in the text of the review. Pooled effect sizes (IOP and IRR) were recalculated and adjusted for the potentially confounding factors of baseline IOP and duration of follow-up.

**Results of the review**

Nine RCTs (n=1,318) were included in the review. Studies evaluating travoprost had, on average, longer follow-up periods (mean 5.1 months) than those evaluating bimatoprost (mean 3.7 months) and latanoprost (mean 4.2 months). The sample size of trials evaluating bimatoprost was lower (mean of 54) than that of trials evaluating travoprost (mean of 64) and latanoprost (mean of 79).

There were no statistically significant differences in mean unadjusted and adjusted IOPs for patients treated with travoprost or bimatoprost, compared with those treated with latanoprost. However, treatment with newer prostaglandins (bimatoprost or travoprost) was associated with a significantly greater decrease in adjusted IOP compared with those treated with latanoprost (-1.00 mmHg, 95% CI: -1.91, -0.10, p=0.03). The adjusted favourable response rate was also 17% higher for patients treated with the newer prostaglandins (bimatoprost or travoprost) compared with latanoprost (IRR 1.17, 95% CI: 1.00, 1.35, p=0.04).

The Egger test and Begg adjusted rank correlation test did not show any evidence of publication bias.

**Authors’ conclusions**

For patients with open angle glaucoma and ocular hypertension, travoprost and bimatoprost may be more effective than latanoprost for lowering the IOP.

**CRD commentary**

This review answered a clearly defined review question. However, it may have failed to include all the relevant data since it excluded unpublished studies and those not published in English or French. The authors’ tests for publication bias suggest that this was not the case, but these tests are unlikely to be reliable given the small number of studies included in the review. It is difficult to assess the risk of reviewer error and bias as the authors did not describe the review methods in detail. They did, however, acknowledge that one limitation of their analysis was the lack of any assessment of study quality. There are several other factors which also make it difficult to assess the reliability of the analysis, including the possible duplication of control group data when pooling studies comparing all three prostaglandins, and the potential errors when estimating the rate of responders. The authors also stated that the studies included varying populations of participants, used various different methods to collect IOP data, and differed in terms of sample size and study duration, dependent on the study drug used. Although some potential confounding factors were considered in the analysis, the authors acknowledged variations between the studies as a limitation. The authors’ conclusions also rely on (to differing extents) indirect comparison data, non significant statistical differences in effect sizes, and effect sizes pooled across different prostaglandin analogues. It should also be noted that the review was funded by a manufacturer of travoprost and the lead author is an employee of the same company. Overall, the aforementioned limitations in the review analysis and methods suggest that the review findings may not be reliable.
Implications of the review for practice and research
Practice: The authors stated that their findings may be useful when 'determining the optimal treatment strategy for individual patients'.

Research: The authors did not state any implications for research.

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.