Efficacy and tolerability of prostaglandin analogs: a meta-analysis of randomized controlled clinical trials

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CRD summary
This review evaluated the intraocular pressure lowering effects and tolerability of latanoprost, bimatoprost, and travoprost in patients with primary open-angle glaucoma or ocular hypertension. The authors concluded that bimatoprost was more effective than the other drugs in reducing intraocular pressure, although conjunctival hyperaemia incidence was higher. This was a well-conducted review and the authors' conclusions are likely to be reliable.

Authors' objectives
To evaluate the intraocular pressure lowering effects and tolerability of latanoprost, bimatoprost, and travoprost.

Searching
MEDLINE, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), the metaRegister of Controlled Trials, and ClinicalTrials.com were searched up to the end of July 2006. Search terms were reported. Reference lists and review articles were searched, and pharmaceutical companies were contacted for additional material.

Study selection
Double blind, randomised controlled trials (RCTs) with intention-to-treat or per protocol data on patients aged at least 18 years, where at least 90% had primary open-angle glaucoma or ocular hypertension, were eligible for inclusion in the review. Patients receiving systemic or ocular medication that could affect intraocular pressure, and those without intraocular laser surgery within the past three months, were excluded.

The outcome of interest was the mean intraocular pressure change between baseline and three months (or after one to six months of treatment where data were not available at three months).

The mean age range of included patients was between 58.8 and 66.5 years, and the proportion of females ranged from 51.5% to 62.5%. The interventions of interest were monotherapies comprising the prostaglandin analogues latanoprost (0.005%, Pfizer inc, New York, NY), travoprost (0.004%, Alcon Inc, Fort Worth, Texas), or bimatoprost (0.03%, Allergan Inc, Irvine, California) administered as one drop per day between 6 PM and 10 PM. The majority of included trials compared bimatoprost with latanoprost. Three or more diurnal intraocular pressure time point measurements were used (8 AM ± 2; 12 PM ± 2; 4 PM ± 2, and/or 8 PM ± 2). Not all trials provided data on all time points. Tolerability was assessed as patient-reported conjunctival hyperaemia at three months (or after one to six months of treatment if data were not available at three months).

Two independent reviewers selected the papers for inclusion in the review. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was assessed using the Jadad score (where 1 is the lowest and 5 is the highest achievable score). The adequacy of allocation concealment was assessed using criteria recommended by Schulz et al, and Juni and Egger. Withdrawals and blinding were also assessed.

It appeared that two independent reviewers assessed the quality of included trials. Disagreements were resolved by consensus.

Data extraction
Data were extracted to calculate the relative risk (RR) for categorical variables, and the weighted mean difference (WMD) for continuous outcomes. 95% confidence intervals (CI) were also calculated. Where standard deviations or standard errors were not reported, these were calculated by the authors.

The authors did not state how many reviewers performed the data extraction.

**Methods of synthesis**
A fixed effect meta-analysis was used to pool the relative risks, weighted mean differences, and 95% confidence intervals using the inverse-variance weighting method. Statistical heterogeneity was assessed using the $X^2$ test (where $p<0.10$ was statistically significant). Sensitivity analyses were carried out to demonstrate the contribution of each RCT to the pooled estimate. Publication bias was assessed using a funnel plot.

**Results of the review**
Eight RCTs ($n=1,610$ patients) were included in the meta-analysis. The authors reported that there was no publication bias. Four trials had a Jadad score of 4, and four trials scored 5 points. Withdrawals ranged from 2.6% to 10.2%.

**Treatment efficacy:** When compared with latanoprost, bimatoprost produced a greater intraocular pressure reduction from baseline at all measured time points. The percentage reduction ranged from 26.98 to 32.88%. The weighted mean differences ranged from 0.50mmHg to 1.17mmHg, and all were statistically significant ($p\leq0.05$). There was no statistically significant heterogeneity. Bimatoprost was more effective than travoprost for intraocular pressure reduction at 8 AM (WMD 1.02mmHg, 95% CI 0.32 to 1.72) and 12 PM (WMD 0.86mmHg, 95% CI 0.12 to 1.59). The percentage reduction ranged from 28.47 to 33.08%. This trend was observed also at 4 PM and 8 PM, but statistical significance was not achieved. There was no statistically significant heterogeneity. Trials of latanoprost versus travoprost showed the two treatments to be comparable in reducing intraocular pressure, with no statistically significant difference at any of the time points measured.

**Treatment tolerability:** Reported conjunctival hyperaemia was higher with bimatoprost when compared with latanoprost (RR 1.70, 95% CI: 1.44 to 2.02) and with travoprost (RR 1.19, 95% CI 1.00 to 1.42). Reported incidences were higher with travoprost compared with latanoprost (RR 1.45, 95% CI 1.22 to 1.72). Absolute incidences were: 0.48 for bimatoprost versus and 0.26 for latanoprost; 0.51 for bimatoprost versus 0.42 for travoprost; and 0.36 for latanoprost versus 0.53 for travoprost. There was no significant heterogeneity in any of the analyses for conjunctival hyperaemia.

**Authors' conclusions**
Bimatoprost was more effective than travoprost and latanoprost in reducing intraocular pressure, although bimatoprost appeared to be less tolerable in terms of reported conjunctival hyperaemia.

**CRD commentary**
This review addressed a clear research question and the inclusion criteria were explicitly reported. The search strategy included a number of relevant sources, and attempts were made to locate unpublished material. Publication bias was assessed and found to be absent. The review process was carried out with sufficient attempts to minimise errors and biases; although it was not clear whether this applied to the extraction of data. A relevant validity assessment tool was used, and trial quality was considered to be high. The chosen method of synthesis was appropriate in the absence of statistical heterogeneity. A discrepancy in the reporting of results was noted for the comparison of travoprost and latanoprost in terms of conjunctival hyperaemia. This aside, the review was generally well-conducted and the authors' conclusions are likely to be reliable.

**Implications of the review for practice and research**
**Practice:** The authors stated that the comparative efficacy of prostaglandin analogues at different time points should be considered when decisions are made to switch treatments in practice. Tolerability outcomes should be considered in patients experiencing side-effects and/or poor compliance.

**Research:** The authors stated that further trials are needed to compare latanoprost with travoprost.
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