Intraocular pressure-lowering effects of all commonly used glaucoma drugs: a meta-analysis of randomized clinical trials


CRD summary
The reviewed aimed to determine the effectiveness of the most frequently prescribed intraocular pressure-reducing agents in patients with glaucoma. The authors' conclusion, that there are multiple options for effective monotherapy in this population, should be viewed with some caution because of incomplete reporting of the review process and limitations in the analysis.

Authors' objectives
To determine the effectiveness of the most frequently prescribed intraocular pressure (IOP)-reducing agents in patients with glaucoma.

Searching
MEDLINE, EMBASE and the Cochrane Controlled Trials Register were searched (up to December 2003) for articles published in English, French, German or Dutch; the search terms were reported. The references of all relevant publications were also checked.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies that compared monotherapeutic, topical administration of IOP-lowering drugs with each other or placebo were eligible for inclusion. The IOP-reducing drugs included in the review were beta-blockers (betaxolol and timolol), prostaglandin analogues or prostanide (bimatoprost, latanoprost and travoprost), an alpha-adrenergic agent (brimonidine), and carbonic anhydrase inhibitors (brinzolamide and dorzolamide). Explicit dosing regimens and frequency of dosing regimens were given. Studies in which treatment drops were administered by either the ophthalmologist or researcher were excluded.

Participants included in the review
Studies in which at least 85% of the participants had a diagnosis of primary open-angle glaucoma or ocular hypertension were eligible for inclusion. Individuals with low tension glaucoma were excluded. Where reported, the mean age of the included participants ranged from 57 to 67 years.

Outcomes assessed in the review
Studies in which the primary end point was change in IOP (peak and trough measurements) from baseline to 1 month were eligible; where 1-month data were not available, the first measurement after 1 month was accepted, up to 6 months. IOP measurements within 3 months after laser or surgery were excluded.

How were decisions on the relevance of primary studies made?
One reviewer made the initial selection from the titles, abstracts and MeSH terms of identified publications. The remaining potentially eligible trials were then randomly distributed between two reviewers, who selected trials for inclusion. The reviewers were blinded to the authors, institution, journal, funding source, and acknowledgements. To evaluate agreement in judgment, 25 articles were selected to be independently reviewed by two of the authors for inclusion or exclusion.
Assessment of study quality
Methodological quality was assessed using the Delphi list, along with several additional items that the authors considered important for interpreting IOP measurements. A maximum of 20 points could be awarded and each item was weighted equally. The authors did not state how the quality of the primary studies was assessed, or how many reviewers performed the quality assessment.

Data extraction
Data were extracted onto a pre-designed form; any ambiguity in the data was resolved by discussion. It was unclear how many reviewers performed the data extraction. In the case of crossover trials, data were extracted only from the period before crossing over of the therapies. Absent absolute values, standard deviations, or change in IOP values were to be calculated for each treatment group where possible.

Methods of synthesis
How were the studies combined?
Pooled absolute and relative changes in IOP values from baseline, along with the 95% confidence interval (CI), were calculated separately for each treatment using a random-effects model. Publication bias was assessed through funnel plots and Egger's measure (based on absolute and relative change from baseline for peak and trough measurements).

How were differences between studies investigated?
The authors did not state whether any formal assessment of heterogeneity was performed. Sensitivity analyses were calculated using only the IOP measurements obtained at 1 month.

Results of the review
Twenty-seven RCTs (n=8,024) were included in the review.

The studies were generally of a high quality. The mean total quality score was 14.2 (interquartile range: 13 to 16).

IOP-lowering effects.

The absolute change from baseline for placebo was -1.3 mmHg at trough and -1.6 mmHg at peak. The absolute change from baseline for glaucoma monotherapy ranged from -4.5 mmHg for brimonidine to -7 mmHg for travoprost at trough, and from -4.4 mmHg for brinzolamide to -8.4 mmHg for brimatoprost at peak. The relative change from baseline for placebo was 5% at both trough and peak. The relative change from baseline ranged from -17% for brinzolamide and dorzolamide to -29% for travoprost at trough, and from -17% for brinzolamide to -33% for bimatoprost at peak. It should be noted that only one eligible trial was found for brinzolamide. These results did not substantially differ when only studies reporting 1-month measurements were included in the analysis.

Funnel plots and Egger's measure did not indicate any publication bias.

Authors' conclusions
Bimatoprost, travoprost, latanoprost and timolol are the most effective IOP-lowering agents in individuals with primary open-angle glaucoma and ocular hypertension. In conclusion, there are multiple options for effective monotherapy in this population.

CRD commentary
The review question was supported by well-defined inclusion and exclusion criteria. Three electronic databases were searched for relevant publications in several languages, and attempts were made to assess publication bias. The methods used to select the primary studies were reported and, although some efforts were made to limit reviewer error or bias, much of this process was carried out by a single reviewer. The procedures used to extract data and assess quality were not, however, well reported; as such, the likelihood of reviewer error or bias could not be fully assessed.
The methodological quality of the primary studies was reported and commented on. Meta-analyses were conducted without any assessment of heterogeneity, so it was not clear if effects were consistent among studies. In addition, it appeared that the data were pooled separately for each treatment, thus the relative effects of different treatments were based on indirect comparisons and any conclusions about the relative effects of treatments are not definitive.

Due to incomplete reporting of the review process and limitations in the synthesis, the authors' conclusions should be viewed with some caution.

**Implications of the review for practice and research**

*Practice:* The authors suggested that as differences between timolol, prostamide and prostaglandin analogues are small, variables such as patient characteristics, quality of life, compliance and costs may be considered when deciding on starting therapy for primary open-angle glaucoma or ocular hypertension.

*Research:* The authors suggested that a future update of this review might be desirable, depending on the number of relevant RCTs published. They also suggested that observational research on the IOP reduction reached by glaucoma medication under typical conditions, rather than clinical conditions, might be useful.

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