Efficacy and tolerability of latanoprost compared to dorzolamide combined with timolol in the treatment of patients with elevated intraocular pressure: a meta-analysis of randomized, controlled trials

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CRD summary
The review found that latanoprost lowered diurnal mean intraocular pressure more than dorzolamide with timolol in patients insufficiently controlled by timolol alone. The treatments were equally effective in patients without baseline timolol treatment. In view of poor reporting and the large number of subgroups reported in the review, the authors’ conclusions require cautious interpretation.

Authors' objectives
To compare latanoprost versus combined dorzolamide plus timolol for treating patients with elevated intraocular pressure.

Searching
The Cochrane Library, PubMed, EMBASE and the Chinese Biomedical Database were searched to April 2008. Search terms were reported. The Internet was searched using Google and Yahoo, along with the websites of relevant associations and their conference sites. Trial registries were also searched and manufacturers were contacted for further data. References of retrieved articles and reviews were handsearched. The search was not restricted by publication status.

Study selection
Randomised or quasi-randomised controlled trials that compared the efficacy of latanoprost monotherapy versus combined dorzolamide plus timolol, administered either concomitantly or as a fixed combination, for treating glaucoma or ocular hypertension were eligible for inclusion. Trials were required to report diurnal mean intraocular pressure reduction (primary outcome) and/or intraocular pressure reduction at 10 am. Tolerability outcomes (withdrawal due to adverse events, total and individual adverse events) were also of interest in the review. Trials of normal-tension glaucoma were excluded.

Most participants in the review had primary open-angle or exfoliative glaucoma. Mean participant age ranged from 54 to 70 years. In a few studies all the participants had received timolol for two to six weeks, but in most studies participants were not receiving treatment at baseline. In all the included studies, 0.005% latanoprost was administered once daily. Most control groups received a fixed combination of dorzolamide 2% and timolol 0.5% twice daily. Trial duration ranged from one to six months, and efficacy outcomes were reported at one, two, three and six months. Trials were conducted in a wide variety of countries.

Two reviewers independently selected the articles, which were checked by a third reviewer.

Assessment of study quality
The authors appeared to use a modified version of the Jadad scale to assess the validity of the included trials, assigning points (up to a maximum of 5) for allocation concealment, blinding, use of intention-to-treat (ITT) analysis, and withdrawals.

Two reviewers independently conducted the assessment.

Data extraction
Relative risks (RRs) were extracted or calculated for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs). Where means and standard deviations were not available, they were...
estimated using methods described in the Cochrane Handbook for Systematic Reviews of Interventions. Intention-to-treat analysis was used, based on all randomised participants who received at least one dose of treatment and had baseline data available. For adverse events, crude event rates from all trials were pooled to calculate overall rates, which were converted into relative risks and 95% confidence intervals.

Two reviewers independently extracted the data, with differences resolved by discussion.

Methods of synthesis
Data for continuous outcomes were combined to calculate weighted mean differences (WMD) and 95% confidence intervals using the DerSimonian and Laird random-effects model. Data were stratified by length of treatment. For dichotomous data, pooled relative risks and 95% confidence intervals were calculated. Statistical heterogeneity was assessed using the $\chi^2$ test. Publication bias was assessed using funnel plots.

Sensitivity analyses were conducted to investigate the impact of individual quality components. Subgroup analyses were conducted by baseline treatment, control treatment and type of administration.

Results of the review
Fourteen randomised controlled trials (RCTs) were included in the review (n=2,149 patients), seven parallel group (n=1,882 patients) and seven-crossover (n=267 patients). Quality scores (out of 5 points) were 5 points (two RCTs), 3 (five RCTs), 2 or 1 (three RCTs each), and 0 (one RCT). Six RCTs used adequate methods of allocation concealment, nine used some form of blinding and six used intention-to-treat analysis. Withdrawal rates ranged from nil to 17% (where reported).

Diurnal intraocular pressure: There was no statistically significant difference in percentage reduction in diurnal mean intraocular pressure between the two treatment groups at any period of follow-up. In subgroup analyses, latanoprost was significantly more effective for this outcome at three months than combined dorzolamide plus timolol among patients insufficiently treated with timolol alone (WMD 3.12% intraocular pressure reduction, 95% CI 0.47 to 5.78; three RCTs). Latanoprost was also significantly more effective for this outcome at three months than concomitantly administered dorzolamide and timolol (WMD 3.07% intraocular pressure reduction, 95% CI 0.64 to 5.50; one RCT).

Intraocular pressure at 10.00 am: There was no statistically significant difference between the treatment groups at any period of follow-up in percentage reduction intraocular pressure at 10.00 am. In subgroup analysis by baseline treatment, combined dorzolamide plus timolol was significantly more effective for this outcome at one month than latanoprost among patients insufficiently treated with timolol alone (WMD -4.14% intraocular pressure, 95% CI -5.78 to -2.50; one RCT). Also at one month, a fixed combination of dorzolamide plus timolol was significantly more effective than latanoprost (WMD -4.67% intraocular pressure, 95% CI -6.44 to -2.91; four RCTs).

Tolerability: Latanoprost was associated with significantly fewer withdrawals from treatment due to adverse events than combined dorzolamide plus timolol (RR 0.34, 95% CI 0.13 to 0.84; four RCTs). There was no statistically significant difference between the treatment groups in ocular adverse event rates (three RCTs).

There was significant statistical heterogeneity for several meta-analyses ($\chi^2$ $p=0.05$ to 0.007) and funnel plots for efficacy were asymmetrical: this was attributed largely to two individual trials.

Sensitivity analyses by quality did not substantially affect the results.

Authors' conclusions
Latanoprost lowered diurnal mean intraocular pressure more than dorzolamide plus timolol in patients insufficiently controlled by timolol alone. The treatments were equally effective in patients without baseline timolol treatment.

CRD commentary
The objectives and inclusion criteria of the review were clear and relevant sources were searched for studies, without restriction by publication status. It was unclear whether the search was limited by language. Steps were taken to
minimise the risk of reviewer bias and error by more than one reviewer independently selecting studies, assessing validity and extracting the data.

The statistical techniques used to combine trial effectiveness outcomes appeared appropriate. However, the method used to pool adverse event rates was not reliable, as it did not allow for differences (e.g. in sample size) between the primary trials. The results of primary trials were not reported; it was unclear which trials were included in individual meta-analyses and several analyses had significant unexplained statistical heterogeneity. The review reported a very large number of subgroup analyses at differing time points, which increased the potential for spurious findings. It was unclear whether all subgroups were pre-specified. The authors’ conclusions appeared to place undue emphasis on a single subgroup (pre-treated patients) at a single time-point.

In view of poor reporting and the large number of subgroups reported in the review, the authors’ conclusions require cautious interpretation.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that pragmatic RCTs, with at least a 12 month follow-up, are required to compare latanoprost versus combined dorzolamide plus timolol. Outcomes should include intraocular pressure reduction, control and response rates, and adverse events. They also noted the need to ascertain the efficacy of latanoprost among patients who fail to respond to dorzolamide plus timolol and to conduct long-term follow-up for serious adverse events.

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