The efficacy and harm of prostaglandin analogues for IOP reduction in glaucoma patients compared to dorzolamide and brimonidine: a systematic review

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CRD summary
This review concluded that latanoprost was superior to dorzolamide but not brimonidine. However, fewer adverse events were found for latanoprost than brimonidine. The authors' conclusions follow from the data presented, but are based on small data sets and as such some caution is advisable.

Authors' objectives
To assess the efficacy and safety of prostaglandin analogues (PGAs) compared to brimonidine and dorzolamide in people with elevated intraocular pressure (IOP).

Searching
MEDLINE, BIOSIS Previews, ToxFile, and EMBASE were searched from inception to October 2006. In addition, the Cochrane database (2006, issue 3), DARE, the Latin American and LILACS were also searched. The authors state that a number of trial registries were searched but do give further details. Search terms were not reported. A search filter restricting for controlled trials, meta-analyses and systematic reviews was used. Websites of regulatory agencies, health technology assessment and near-technology assessment agencies, internet search engines and websites of professional associations were also searched. Manufactures of relevant pharmacological agents were contacted. Only articles published in English were included.

Study selection
Studies of randomised controlled trials (RCTs) of adults with raised IOP that compared monotherapy PGA(s) with placebo or another IOP lowering agent (brimonidine or dorzolamide) and a follow-up of at least three months were eligible for inclusion in the review. Included participants were required to be treatment naive or have had a sufficient wash-out period prior to treatment. Trials evaluating patients with closed-angle glaucoma were excluded. Latanoprost was the only PGA assessed (dosages not reported). Length of treatment ranged from three to six months. The main outcome of interest was reduction of IOP (mm Hg) at a minimum of three months follow-up. Secondary outcomes of interest included adverse events, slowing or stop in the progression of visual field defects, slowing or stop in the increase in cupping of the optic nerve, lack of response or loss of therapeutic effect and withdrawals due to adverse events. The majority of studies included a mixed population of patients who were treatment naive, had received previous treatment with an IOP-lowering agent and had failed prior therapy. The included population was predominantly Caucasian. Reported outcomes included change in IOP from baseline (in most studies this was diurnal IOP) and adverse events. IOP was measured using the Goldmann applanation tonometry in all studies.

Two reviewers independently screened papers for inclusion in the review. Disagreements were resolved by consensus.

Assessment of study quality
The quality of the included studies was assessed using the Jadad Scale (maximum score = 5) plus an additional item for allocation concealment. Two authors assessed the validity of the included studies.

Data extraction
Weighted mean differences (WMDs) (mean IOP reduction), relative risks (RRs) and risk differences (RDs) (adverse events) were calculated with their 95 per cent confidence intervals (CI). The number needed to harm (NNH) was also calculated for reported adverse events. Where reported, intention-to-treat (ITT) analysis (defined as participants who received at least one treatment and had at least one evaluation following treatment) was used. One reviewer extracted data from the included studies, which were checked independently by another reviewer.

Methods of synthesis
Studies were combined in a meta-analysis using a fixed-effect model unless significant evidence of statistical
heterogeneity was found, in which case data were summarised using a random-effects model. Statistical heterogeneity was assessed using $I^2$ statistic (>25% was taken to indicate moderate to high heterogeneity) and the $X^2$ test. Sub-group analysis (length of follow-up) and sensitivity analyses (study quality – excluding studies with a score of <3 – and use of ITT analysis) were planned. A descriptive summary was presented for data that were unsuitable for pooling.

**Results of the review**

It is not clear how many studies or participants were included in the review; seven RCTs (n=1,178) were included in the meta-analyses. Two RCTs were considered to be of high quality (Jadad score =5), five RCTs received a Jadad score of 2. Two studies clearly reported use of ITT analysis. Where reported, four studies were industry funded.

**Reduction in IOP at three months post-treatment**

No statistically significant difference in mean IOP was found between those receiving latanoprost and those receiving brimonidine (WMD -1.04, 95% CI: -3.01, 0.93) (3 RCTs, n=471). Evidence of significant statistical heterogeneity was found. The inclusion of only higher quality studies did not change this result significantly.

A statistically significant mean reduction was found in favour of latanoprost compared with dorzolamide (WMD -2.64, 95% CI: -3.25, -2.04, p<0.00001) (3 RCTs, n=328). There was no evidence of significant statistical heterogeneity. All studies were of low study quality.

**Adverse events**

The relative risk of ocular AEs (excluding hyperaemia) was significantly lower in those receiving latanoprost compared with brimonidine (RR 0.66, 95% CI: 0.52, 0.83, p<0.0005) (3 RCTs, n=803). NNH was 9 (95% CI: 6, 20). No significant between group differences were found for any of the other adverse event reported.

**Second line therapy**

One study (n=375) comparing latanoprost with brimonidine in patients with glaucoma or ocular hypertension inadequately controlled with monotherapy or dual therapy; 76% of those treated with latanoprost and 53% of those treated with brimonidine obtained a mean IOP reduction of at least 20 per cent from baseline to six months post-treatment. The mean IOP reduction was 1.9 mm Hg in favour of latanoprost (p<0.001).

**Authors' conclusions**

Latanoprost was found to be more effective than dorzolamide, but not brimonidine. However, fewer adverse events were found for latanoprost than brimonidine. Neither travoprost or bimatoprost were compared with dorzolamide or brimonidine.

**CRD commentary**

The review question was supported by clear inclusion criteria. Several sources were searched for relevant published and unpublished papers. The search was restricted by language and as such may have missed some relevant studies. Methods used to select papers, extract data and assess study validity are likely to have minimised the possibility of reviewer error or bias. The quality of the included studies was assessed and total scores were reported. Greater study detail in terms of population and intervention might have been useful. Standard methods were used for pooling studies. The authors planned subgroup and sensitivity analyses, although this was not always possible to perform. The authors highlighted that none of the studies were of long enough duration to detect changes in either optic nerve or visual field. The authors' conclusions follow from the data presented, but are based on small data sets and as such some caution is advisable.

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**Bibliographic details**

Practice: the authors state that current PGAs are well tolerated.

Research: the authors state that long term studies evaluating the impact of PGAs on clinical outcomes are needed.

Indexing Status
Subject indexing assigned by NLM

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Adult; Aged; Antihypertensive Agents /adverse effects /therapeutic use; Brimonidine Tartrate; Female; Glaucoma /drug therapy; Humans; Male; Middle Aged; Prostaglandins F, Synthetic /adverse effects /therapeutic use; Prostaglandins, Synthetic /adverse effects /therapeutic use; Quinoxalines /therapeutic use; Randomized Controlled Trials as Topic; Sulfonamides /therapeutic use; Thiophenes /therapeutic use; Treatment Outcome

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Record Status
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.