Efficacy of antiglaucoma fixed combination therapy versus unfixed components in reducing intraocular pressure: a systematic review

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CRD summary
This review concluded that fixed combination therapies were equally as safe and effective at lowering intraocular pressure as their individual components administered separately. The conclusions about efficacy are reasonable, but their reliability was dependent upon the appropriateness of the cut-off point used to establish equal effectiveness. The conclusions about equal safety were based on limited data.

Authors’ objectives
To evaluate the efficacy of fixed combination ocular hypotensive therapies compared to their non-fixed components used concomitantly, for lowering intraocular pressure in glaucoma and ocular hypertension.

Searching
MEDLINE, EMBASE and Cochrane Controlled Trials Register were searched from 1996 onwards without language restrictions. The search terms and date when the searches ended were not reported. Conference abstracts and references from relevant articles were searched.

Study selection
Randomised controlled trials (parallel and crossover) of at least 12 weeks duration that compared fixed medications to their non-fixed components administered separately were included. The specific medications of interest were a beta-blocker plus one of travoprost, brimonidine tartrate, dorzolamide, bimatoprost and latanoprost. The population of interest was adults with glaucoma or ocular hypertension with a baseline intraocular pressure of 22mmHg or more. The primary outcome of interest was mean change in intraocular pressure from baseline to 12 weeks. The secondary outcome was adverse events, including discontinuation due to adverse effects.

The included studies investigated four of the five combinations of interest. A single study that compared fixed and non-fixed administration of bimatoprost plus beta-blocker was excluded due to its short duration of treatment (three weeks). Where reported, most participants had primary open-angle glaucoma and the mean age of participants ranged from 61 to 65 years old. The studies were all multicentre, predominantly in Western countries and were published between 1998 and 2007.

The authors stated neither how the papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
A checklist based on the Critical Appraisal Skills Programme (CASP) assessment tool and the Cochrane Eyes and Vision Group criteria were used. Ten criteria were scored as inadequate (1 point), unclear (2 points) or adequate (3 points); the maximum score was 30 points. The authors did not state how the validity assessment was performed.

Data extraction
The mean difference between groups in change from baseline to 12 weeks and 95% confidence intervals (CI) for intraocular pressure were extracted for three measurement points, where available: baseline (before morning dose); after two hours; and after eight hours. The number of adverse events was also extracted. Data were extracted using a standardised form. The authors did not state how many reviewers extracted data.

Methods of synthesis
Studies were pooled using a fixed-effect meta-analysis, provided heterogeneity tests were not statistically significant. As a sensitivity analysis, studies that reported intention to treat data and studies that reported per protocol data were pooled separately and the results compared.
Fixed and non-fixed therapy were concluded to have equal efficacy if the upper limit of the 95% CI was 1.5mmHg or less.

The Begg and Egger tests were used to assess for publication bias.

**Results of the review**

Seven RCTs (2,083 eyes, range 32 to 517) were included. The studies were generally of high quality: all were double blind; six reported observer masking; six reported a computer-generated randomisation schedule; and all used calibrated Goldmann tonometry with intraocular pressure measured at least twice at each time point.

At all the assessment periods, the pooled results fell below the non-inferiority level of 1.5mmHG. This suggested that fixed therapy was non inferior (had similar efficacy) to non-fixed therapy for reducing intraocular pressure.

There was a statistically significant difference between fixed and non-fixed therapies that favoured non-fixed therapies at two hours (mean difference 0.39, 95% CI: 0.04 to 0.75; six trials) and at eight hours (mean difference 0.50, 95% CI: 0.16 to 0.85; four trials), but not at baseline (mean difference 0.20, 95% CI: -0.11 to 0.51; six trials). Sensitivity analysis that compared intention to treat and per protocol data did not alter the results. There was no evidence of heterogeneity at any time point.

The main adverse effects were hyperaemia, ocular irritation and keratitis. One study reported significantly more cases of hyperaemia in the fixed compared to the non-fixed therapy group. In five studies there was a higher number of discontinuations due to intolerance in the fixed therapy group (1% to 12.5%).

The authors stated that the funnel plots showed no evidence of publication bias.

**Authors’ conclusions**

Fixed combination therapies were equally as safe and effective at lowering intraocular pressure as their non-fixed components administered concomitantly.

**CRD commentary**

This review had a clearly stated review question and inclusion criteria. A number of relevant databases were searched and attempts were made to identify unpublished and non-English language studies. The tests for publication bias were not statistically significant, although the authors rightly cautioned that the robustness of the tests was limited by the small number of studies available. It was unclear whether more than one researcher was involved in study selection, data extraction and quality assessment, therefore, there may have been a risk of error and bias in the review processes. The statistical analysis was appropriate and there was no evidence of statistical heterogeneity. The authors conclusions about efficacy were reasonable, but the reliability of the conclusions was dependant upon the appropriateness of the cut-off point used to establish equal efficacy. Given the limited data available on adverse events, the conclusions about equal safety should be treated with caution.

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

Practice: The authors stated that where patients required a multiple medication regime, fixed combination therapies were as effective as their non-fixed components administered concomitantly.

Research: The authors stated that studies with longer follow-up periods were required to assess glaucoma progression and long-term adverse effects and patient progression.

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