Meta-analysis of randomized controlled trials comparing timolol with brimonidine in the treatment of glaucoma

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CRD summary
The authors concluded that timolol and brimonidine were equally effective in lowering intraocular pressure. Brimonidine was associated with a higher rate of allergy. The review was mostly well conducted but, in view of unexplained heterogeneity in the analyses, the authors' conclusions may need to be regarded with some caution.

Authors' objectives
To compare the efficacy and tolerability of timolol with brimonidine in the treatment of glaucoma.

Searching
The following databases were searched: MEDLINE (1966 to December 2006), EMBASE (1980 to December 2006), the Cochrane Central Register of Controlled Trials and the Science Citation Index Expanded. The MEDLINE search string was provided. The reference lists of selected studies were also checked. There was no restriction by language or publication status.

Study selection
Randomised controlled trials (RCTs) and pseudo-randomised controlled trials comparing 5% timolol with 2% brimonidine for the treatment of glaucoma were eligible for inclusion. Included trials were required to report the efficacy and/or tolerability in patients of any age and treatment duration of at least one month. The efficacy outcome of interest was peak intraocular pressure reduction if calculable, otherwise mean intraocular pressure reduction. Studies with a qualitative focus were also eligible but were to be reported separately. Studies comparing combinations of drugs were excluded.

The mean age of participants in the included studies ranged from 58 to 69 years. Nearly all had either open-angle glaucoma or ocular hypertension and just over half were female (where reported). All studies excluded patients with contraindications to beta-blockers. In all studies (where reported) participants were either treatment naive or had a washout period. The interventions were administered twice daily as monotherapy. Outcomes were measured with the Goldmann applanation tonometer. Tolerability outcomes in most cases included ocular itch/discomfort/burning and ocular allergy. Duration of follow up ranged from one to 36 months. All studies were conducted in the USA or Taiwan.

Two authors independently selected studies for inclusion.

Assessment of study quality
The following aspects of study validity were evaluated: allocation concealment; blinding of patient and investigator; methods for measuring outcomes; withdrawal rates; handling of withdrawals in analysis.

Two authors independently conducted the assessment. Disagreements were resolved by discussion or in consultation with a third author.

Data extraction
Odds ratios (ORs) were calculated for dichotomous outcomes and mean differences for continuous outcomes, with 95% confidence intervals (CIs). If necessary the authors calculated IOPRs and standard deviations from data reported in other formats, using formulae reported in the review. Data were reported by intention to treat (ITT) if possible; if not, analysis was restricted to available cases.

Two reviewers independently extracted the data using a standardised format. Disagreements were resolved by discussion or in consultation with a third author. Study investigators were contacted for more information about trial methodology.
Methods of synthesis
Data were combined using random effects models to calculate weighted mean differences (WMDs) and 95% CIs. The Cochrane Q test and the I² statistic were used to assess heterogeneity. Prespecified subgroup analysis was conducted to check whether study duration or sample size affected outcomes. In addition, meta-regression was used to check the impact of study duration, allocation concealment and sample size. Publication bias was assessed with a funnel plot.

Results of the review
Eight parallel-group studies (ten articles) were included in the review, all apparently RCTs (2,387 patients, range 40 to 774) and all published in English. Seven studies reported adequate allocation concealment and double blinding; withdrawal rates ranged from nil to 18% (where stated) and eight studies reported using ITT analysis or carrying the last observation forwards.

Timolol versus brimonidine (eight studies): When all studies were combined, the mean intraocular pressure reduction did not differ significantly between the groups (WMD 0.24mmHg, 95% CI -0.57 to 1.04). This finding had significant heterogeneity (p=0.00001, I²=91%). Subgroup and meta-regression analyses of efficacy outcomes suggested that studies with at least 100 participants, which were those more likely to have adequate allocation concealment, slightly favoured brimonidine.

Adverse effects: The risk of adverse effects (burning and stinging) did not differ significantly between the groups (RR 1.14, 95% CI 0.61 to 2.14) but a significantly lower risk of allergy was associated with timolol (RR 0.08, 95% CI 0.01 to 0.47, p=0.005).

One study reported a chronotropic effect with timolol (p=0.04, 211 patients).

Other outcomes: Individual studies found that brimonidine was associated with a significantly improved between- or within-group outcome for retinal nerve fibre layer damage (41 patients; p≤0.02), and contrast sensitivity (16 patients, p≤0.046).

There was no obvious evidence of publication bias.

Authors' conclusions
Timolol and brimonidine were equally effective in lowering intraocular pressure. Brimonidine was associated with a higher rate of allergy.

CRD commentary
The review objectives and inclusion criteria were mostly clear, although there were initial references to the inclusion of two qualitative studies that were not mentioned subsequently. The literature search was thorough and without publication or language restriction. Steps were taken to minimise bias and error by having more than one reviewer independently involved in study selection, data extraction and validity assessment.

Relevant criteria were used to assess study quality, although it was not completely clear whether all studies were RCTs or whether some were pseudo-randomised. The plan to combine the studies statistically appeared reasonable and appropriate statistical methods were used to pool data and to assess for heterogeneity and publication bias. However, it was unclear why one analysis differed by using a fixed effect model. Although the authors noted that the main analysis had significant heterogeneity, they did not acknowledge the very marked heterogeneity also evident in all the other analyses. Methodological differences between the studies were investigated but these did not appear to account for the heterogeneity; possible clinical differences were not explored. In view of this unexplained heterogeneity, the reliability of the pooled results is questionable.

The review was well conducted but, in view of this unexplained heterogeneity in the analyses, the authors’ conclusions may need to be regarded with some caution.

Implications of the review for practice and research
Practice: The authors stated that since timolol and brimonidine appeared equally effective in lowering intraocular pressure, considerations such as tolerability, compliance, cost and non-intraocular pressure related factors may be decisive factors in choosing which drug to prescribe.
Research: The authors did not make any recommendations for research.

Funding
Not stated.

Bibliographic details

PubMedID
18412600

DOI
10.1111/j.1442-9071.2008.01720.x

Original Paper URL

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic alpha-Agonists /adverse effects /therapeutic use; Adrenergic beta-Antagonists /adverse effects /therapeutic use; Brimonidine Tartrate; Glaucoma /drug therapy; Humans; Quinoxalines /adverse effects /therapeutic use; Randomized Controlled Trials as Topic; Timolol /adverse effects /therapeutic use; Treatment Outcome

AccessionNumber
12008103729

Date bibliographic record published
01/12/2008

Date abstract record published
31/03/2009

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.