Treatment of ocular hypertension and open angle glaucoma: meta-analysis of randomised controlled trials

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Abstract

Objective Open angle glaucoma is one of the most common causes of blindness in industrialised nations. Treatments to lower ocular pressure are widely used in glaucoma prevention and treatment, despite conflicting evidence.

Design We performed meta-analyses to reassess the effectiveness of pressure lowering treatment to delay the development of glaucoma in ocular hypertension, as well as progression of manifest open angle glaucoma.

Data sources Medline, Embase, and the Cochrane Library.

Selection of studies Eligible studies were randomised controlled trials with a concurrent untreated control group and information on time to glaucomatous changes to visual field and optic disc. Trial reports were reviewed independently by two investigators in an unblinded standardised manner.

Results Meta-analysis of trials in ocular hypertension showed a significant preventive effect of reducing intraocular pressure on progression to glaucoma (hazard ratio 0.56, 95% confidence interval 0.39 to 0.81, P = 0.01; number needed to treat 12). Pooled data of studies in manifest glaucoma showed a significant delay of visual field deterioration (0.65, 0.49 to 0.87, P = 0.003; NNT = 7), with subgroup analysis showing a larger effect in patients with raised pressure and a reduced effect in normal tension glaucoma (subgroup comparison: not significant).

Conclusions Lowering intraocular pressure in patients with ocular hypertension or manifest glaucoma is beneficial in reducing the risk of visual field loss in the long term.

Introduction

Glaucoma is characterised by an acquired loss of retinal ganglion cells and atrophy of the optic nerve. As increased intraocular pressure may or may not be present,[1] the diagnosis of open angle glaucoma is now based only on glaucomatous visual field defects or typical changes of the optic disc (table). However, raised intraocular pressure remains an important risk factor for the development of primary open angle glaucoma.[2] Since symptoms present late, interventions at an early stage of the disease promise to be most effective, for example, in patients with ocular hypertension (table 1). However, because most people with ocular hypertension will not develop glaucoma[3] and a prior meta-analysis was unable to show a significant effect,[4] preventive therapy has been controversial. If early visual field loss has occurred or the optic disc has typical glaucomatous changes, then treatment to lower the intraocular pressure is initiated in virtually all patients. Since this approach includes patients with normal tension glaucoma, a relative, rather than absolute, reduction of intraocular pressure (for example, 20%) is the initial target.

The primary objective was to review systematically the literature with regard to the effectiveness of treatment of ocular hypertension and open angle glaucoma (both primary open angle glaucoma and normal tension glaucoma).

Table 1 Definitions of glaucoma and ocular hypertension

Pathology	Ocular hypertension	Open angle glaucoma	
		Primary open angle glaucoma	Normal tension glaucoma
Raised intraocular pressure	Yes	Yes	No
Optic disc changes or visual field defects, or both	No	Yes	Yes
Symptoms	No	<50% at diagnosis	<50% at diagnosis

Methods

Databases searched included the Cochrane Central Register of Controlled Trials (2004), Medline (1966-2004), and Embase (1974-2004). We searched other databases for guidelines and health technology assessment reports covering glaucoma. We also searched reference lists of relevant articles and the Science Citation Index. For ongoing trials we contacted investigators and experts. The search was not restricted to specific languages or years of publication. See bmj.com for search strategy.

Study selection

We included only randomised controlled trials of pressure lowering treatment (medical and surgical) with a concurrent untreated control group and appropriate end points, such as glaucomatous visual field defects or glaucomatous changes to the optic disc, with follow up for at least a year.

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Description of studies

Literature search yielded 1213 reports, which consisted mostly of studies comparing one drug with another. Two authors reviewed retrieved abstracts independently in an unblinded standardised manner. We then critically appraised relevant articles and extracted data independently. We resolved disagreements by discussion. Five studies included a total of 2326 patients with ocular hypertension who were randomly assigned to various pressure lowering eye drops compared with placebo. Two studies in patients with manifest glaucoma (total: 400) used either eye drops or surgical approaches to lower intraocular pressure. See bmj.com for details of studies.

Data extraction and analysis

We extracted data using a standardised form. We included only patients with unequivocal glaucomatous changes to the visual field or optic disc. We extracted information on the time to definite visual field deteriorations and optic disc changes compatible with open angle glaucoma. We performed separate meta-analyses for ocular hypertension and for open angle glaucoma, as well as predefined subgroup analysis of normal tension glaucoma compared with increased pressure glaucoma. We assessed heterogeneity and carried out sensitivity analysis using the random and fixed effects model, as well as the pre-defined subgroup analysis of elevated and normal tension glaucoma. We calculated the number needed to treat to prevent the first glaucomatous visual field defect in patients with ocular hypertension and glaucoma progression in patients with open angle glaucoma within five years after treatment onset.

Results

Combining the results of the five trials for the treatment of patients with ocular hypertension alone showed a beneficial pressure lowering treatment effect (hazard ratio 0.56, 95% confidence interval 0.39 to 0.81, P = 0.01; fig 1). We could not observe significant heterogeneity of the included studies ($\chi^2 = 6.2$, P = 0.185; $I^2 = 35.4\%$, 95% confidence interval 0 to 75.8%).

To illustrate the baseline risk, estimates in the control group for remaining free of glaucomatous visual field defects within five years after treatment onset ranged from approximately 63% to 91% in the five trials. Using the 80% mark as a realistic assumption and the estimated hazard ratio of 0.56, we calculated that 12 patients with ocular hypertension alone need to be treated to prevent the first glaucomatous visual field defect or definite glaucomatous disc change within five years of treatment (95% confidence interval for number needed to treat 9 to 29).

Treatment of open angle glaucoma with and without raised intraocular pressure

Combining the results from the two recent randomised controlled trials in manifest open angle glaucoma showed a significant pooled treatment effect of lowering intraocular pressure to effectively prevent glaucoma progression (hazard ratio 0.65, 95% confidence interval 0.49 to 0.87, P = 0.003; fig 2[2]). The included studies were not significantly heterogeneous ($\chi^2 = 0.13$, P = 0.72).

The estimates in the control group for remaining free of glaucoma progression within five years after treatment onset were 42% and 43%. Accordingly, when using the 40% mark and the estimated hazard ratio of 0.65, seven patients with glaucoma need to be treated to prevent one patient with glaucoma progression within five years of treatment (95% confidence interval for number needed to treat 4 to 20).

Sensitivity and subgroup analysis

Changing our meta-analysis model from random to fixed effects did not change the results in either meta-analysis. The subgroup of patients with elevated ocular pressure glaucoma responded well to pressure lowering treatment, as seen in a subgroup analysis of these patients in the early manifest glaucoma trial (hazard ratio 0.57, 95% confidence interval 0.37 to 0.89, P = 0.013). When we calculated whether the subgroup of patients with normal tension glaucoma would fare equally well as all patients with open angle glaucoma, the overall effect did not reach significance and the confidence interval remained wide, indicating uncertainty about the true treatment effect. However, when we used methods described by Altman and Bland,[12] to compare these two subgroups we found no significant difference.

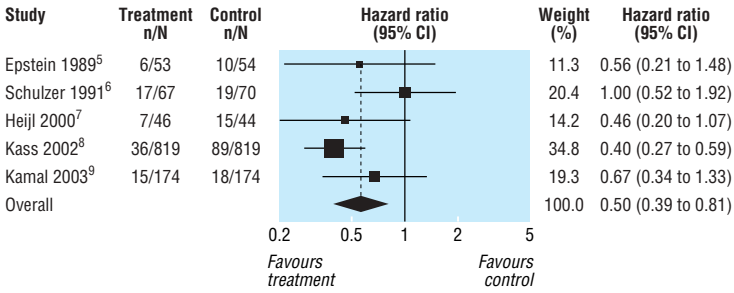

Fig 1 Visual field loss or deterioration of optic disc, or both, among patients randomised to pressure lowering treatment *v* no treatment in ocular hypertension. Hazard ratios of less than 1.0 favour pressure lowering treatment. Boxed area is proportional to weight given to each trial in the statistical model. Heterogeneity: χ^2=6.2 (P=0.185); I^2=35.4% (95% confidence interval 0 to 75.8%)

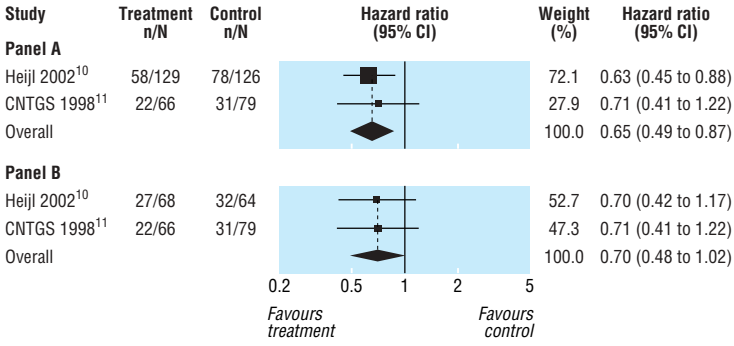

Fig 2 Visual field loss or deterioration of optic disc, or both, among patients randomised to pressure lowering treatment *v* no treatment in open angle glaucoma (panel A). Panel B shows subgroup analysis of data in normal tension glaucoma. Hazard ratios of less than 1.0 favour pressure lowering treatment. Boxed area is proportional to weight given to each trial in the statistical model. Heterogeneity: χ^2=0.13 (P=0.72) for open angle glaucoma and χ^2=0.001 (P=0.97) for normal tension glaucoma

Discussion

Primary prevention of glaucomatous visual field defects in patients with ocular hypertension by using topical pressure lowering agents seems to be effective, as shown in this meta-analysis of five methodologically adequate trials. A 1993 meta-analysis of randomised controlled trials[4] identified only three appropriate randomised controlled trials, out of a total of 102 trials. Although the pooled treatment effect showed a reduced risk for progression to glaucoma, the 95% confidence interval was wide, indicating that worsening of visual field defects could not be excluded in the intervention group.

The recent ocular hypertension treatment study had to exclude 1692 of 3328 patients screened for inclusion in the study for various reasons.[8] The overall effectiveness of treatment may therefore be different in real practice. Moreover, the effectiveness of the investigators' treatment strategy in patients with mildly raised intraocular pressure (above 21 mm Hg, but below 24 mm Hg) remains unanswered.

The results of our meta-analysis, as well as the early manifest glaucoma trial[10 13] show that reducing the intraocular pressure in patients with open angle glaucoma leads to a significant delay of visual field loss, particularly for those patients with increased intraocular pressure, as seen in the subgroup analysis of these patients.

In normal tension glaucoma, lowering the intraocular pressure may be beneficial as seen in the normal tension glaucoma study,[11] but this has to be confirmed by larger trials and newer treatment modalities, because in this study, the development of excess cases of cataracts may have offset the treatment effect. In addition, we were not able to show a significant treatment effect in our subgroup analysis probably because of low power.

Limitations

Firstly, we cannot fully exclude publication bias. However, we did not impose restrictions by language or year of publication, and the search results were complemented by hand searching. Secondly, since our meta-analysis would lose significance by excluding the ocular hypertension treatment study,[8] the overall beneficial effect can only be safely assumed in patients with intraocular pressure of 24 mm Hg or more. Four of five included studies on ocular hypertension had high dropout rates, and therefore the magnitude of effect may have been biased.

Although the more recent trials seem methodologically sound, some general questions remain. It is not entirely clear why some patients may experience disease progression much faster than others (with and without treatment), even if they do not differ in terms of their risk factor profile. More research is needed to identify these subgroups.

Conclusions

Although lowering the intraocular pressure in patients with ocular hypertension of 24 mm Hg or more to prevent progression to primary open angle glaucoma seems to be beneficial, uncertainty prevails about the optimal treatment for patients with slightly raised intraocular pressure of 22 mm Hg or 23 mm Hg. In general, patients with manifest open angle glaucoma showed a significant delay in progression of visual field deterioration when treated with a pressure lowering strategy. More research is needed in the subgroup of patients without increased intraocular pressure to determine which patients with normal tension glaucoma will benefit most.

What is already known on this topic

Primary open angle glaucoma is a leading cause of blindness in industrialised countries

Lowering intraocular pressure is generally used to prevent and to treat primary open angle glaucoma, although a meta-analysis of trials on ocular hypertension did not show a significant preventive treatment effect

What this study adds

Medical reduction of ocular pressure seems to be beneficial for the primary prevention of glaucomatous visual field defects

Only one adequate trial has shown effective secondary prevention of visual field deterioration with topical treatment or surgery in patients with manifest primary open angle glaucoma

A meta-analysis summarising data on normal tension glaucoma was inconclusive

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1 Dielemans I, Vingerling JR, Wolfs RC, Hofman A, Grobbee DE, de Jong PT. The prevalence of primary open-angle glaucoma in a population-based study in the Netherlands. The Rotterdam study. *Ophthalmology* 1994;101:1851-5.
2 Gordon MO, Beiser JA, Brandt JD, Heuer DK, Higginbotham EJ, Johnson CA, et al. The ocular hypertension treatment study: baseline factors that predict the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:714-20.
3 Kitazawa Y, Horie T, Aoki S, Suzuki M, Nishioka K. Untreated ocular hypertension. A long-term prospective study. *Arch Ophthalmol* 1977;95:1180-4.
4 Rossetti L, Marchetti I, Orzalesi N, Scorpiglione N, Torri V, Liberati A. Randomized clinical trials on medical treatment of glaucoma. Are they appropriate to guide clinical practice? *Arch Ophthalmol* 1993;111:96-103.
5 Epstein DL, Krug JH, Jr, Hertzmark E, Remis LL, Edelstein DJ. A long-term clinical trial of timolol therapy versus no treatment in the management of glaucoma suspects. *Ophthalmology* 1989;96:1460-7.
6 Schulzer M, Drance SM, Douglas GR. A comparison of treated and untreated glaucoma suspects. *Ophthalmology* 1991;98:301-7.
7 Heijl A, Bengtsson B. Long-term effects of timolol therapy in ocular hypertension: a double-masked, randomised trial. *Graefes Arch Clin Exp Ophthalmol* 2000;238:877-83.
8 Kass MA, Heuer DK, Higginbotham EJ, Johnson CA, Keltner JL, Miller JP, et al. The ocular hypertension treatment study: a randomized trial determines that topical ocular hypotensive medication delays or prevents the onset of primary open-angle glaucoma. *Arch Ophthalmol* 2002;120:701-13.
9 Kamal D, Garway-Heath D, Ruben S, O'Sullivan F, Bunce C, Viswanathan A, et al. Results of the betaxolol versus placebo treatment trial in ocular hypertension. *Graefes Arch Clin Exp Ophthalmol* 2003;241:196-203.
10 Heijl A, Leske MC, Bengtsson B, Hyman L, Hussein M. Reduction of intraocular pressure and glaucoma progression: results from the early manifest glaucoma trial. *Arch Ophthalmol* 2002;120:1268-79.
11 The effectiveness of intraocular pressure reduction in the treatment of normal-tension glaucoma. Collaborative Normal-Tension Glaucoma Study Group. *Am J Ophthalmol* 1998;126:498-505.
12 Altman DG, Bland JM. Interaction revisited: the difference between two estimates. *BMJ* 2003;326:219.
13 Leske MC, Heijl A, Hussein M, Bengtsson B, Hyman L, Komaroff E. Factors for glaucoma progression and the effect of treatment: the early manifest glaucoma trial. *Arch Ophthalmol* 2003;121:48-56.

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