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Relationship Between Intraocular Pressure and Preservation of Visual Field in Glaucoma

Ivan Goldberg, FRANZCO, FRACS

Sydney Eye Hospital and the Save Sight Institute, University of Sydney, Sydney, Australia

Abstract. Intraocular pressure (IOP) correlates with progressive loss of visual field in patients with glaucoma. Decreasing IOP has been proven to reduce progressive loss of the visual field. This is true both for glaucoma patients with IOPs above or within the normal range. For individuals with ocular hypertension (high IOP but no evidence of glaucomatous neuropathy), lowering IOP may reduce the risk of developing glaucoma. This article reviews scientific evidence that supports the importance of lowering IOP in patients with glaucoma or ocular hypertension. (**Surv Ophthalmol 48 [Suppl 1]**:S3–S7, 2003. © 2003 Elsevier Science Inc. All rights reserved.)

Key words. glaucoma • intraocular pressure • visual field loss

Introduction

Glaucoma is a major cause of blindness throughout the world. Between 67 million[8] and 105 million[25] people are estimated to have glaucoma worldwide. In the United States alone, approximately 3 million people have glaucoma, although only half of them are aware of their condition.[9]

An English oculist, W. Mackenzie, first suggested the role of increased intraocular pressure (IOP) in glaucoma in 1835. For 150 years physicians have prescribed ocular hypotensive agents for their glaucoma patients, even before they understood why the drugs worked.[6,21]

With the introduction of the Zeiss slit-lamp in 1920 and the Troncoso gonioscope in 1925, ophthalmologists could examine the anatomy of the glaucomatous eye and begin to understand the pathophysiology of the glaucomatous process. These technologies enabled physicians to distinguish primary open-angle from angle-closure glaucoma, and to develop and to test hypotheses as to why certain drugs worked in some patients and not in others. Gradually, an understanding of the relationship between IOP and glaucomatous visual field loss began to emerge.

This article reviews some of the scientific evidence that supports the importance of lowering IOP in patients with glaucoma or ocular hypertension (OHT). It is not exhaustive.

Relationship Between Intraocular Pressure and Visual Field Loss

The correlation between IOP and visual field defects has been recognized for over 20 years.[19] From epidemiological studies, the prevalence of glaucoma is known to increase with higher IOP. In a population-based prevalence survey of more than 5,000 individuals aged 40 and over in Baltimore, participants who had a screening IOP greater than 30 mm Hg were over 38 times more likely to have glaucoma (as defined in the study) than individuals with an IOP below 15 mm Hg.[24] The Australian Blue Mountains Eye Study (P. Healey, personal communication, data

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as yet unpublished) found the odds ratio of developing glaucoma was 4.7 times higher in patients with a screening IOP of greater than 21 mm Hg than in patients with lower IOPs, and the odds of developing glaucoma were 2.8 times higher in patients with IOP asymmetry between left and right eyes of greater than 3 mm Hg than in patients with smaller IOP asymmetry. So the level of IOP is directly related to the likelihood of glaucoma.

In addition, reducing IOP in glaucoma patients limits its disease progression and slows visual field loss. The Advanced Glaucoma Intervention Study (AGIS)[1] is one of the most widely cited long-term studies of glaucoma progression and its relationship to IOP. Following patients with definite glaucomatous visual field abnormalities and an inadequate response to maximal tolerable medical therapy, the investigators randomized patients to undergo sequentially either trabeculectomy–Argon laser trabeculoplasty–trabeculectomy or Argon laser trabeculoplasty–trabeculectomy–trabeculectomy, and additional medications as necessary. They measured IOPs every 6 months for up to 8 years following surgery to reduce IOP. In the predictive analysis, the mean visual field loss from baseline measured in eyes with a mean IOP between 14 mm Hg and 17.5 mm Hg over the first three visits was three times that of eyes with a mean IOP less than 14 mm Hg for these visits (Fig. 1). Similarly, visual fields worsened more in eyes with a mean IOP of 17.5 mm Hg than in eyes with a mean IOP $<$ 14 mm Hg over the first three visits.

In this population, the differences in the rate of visual field loss were not seen until 4 years of follow-up. Because the relationship demonstrated between IOP reduction and visual field progression was based on data analyzed in a post-hoc fashion, there is an inherent inability for this study to randomize the eyes followed to different degrees of IOP reduction. Despite these limitations, the clinical implications of this study are profound: IOP levels that are often considered adequate goals of treatment (near 17 mm Hg) were associated with more progressive visual field loss than were lower IOP levels.

A smaller study by Mao and associates of patients with early primary open-angle glaucoma[16] also showed that patients with lower IOPs on treatment were less likely to progress (over 4 to 11 years of follow-up), compared with patients that had higher IOPs. All eyes with an average IOP less than 17 mm Hg during follow-up remained stable, while all eyes with an average IOP over 21 mm Hg had progressive optic disk cupping or visual field loss or both (Fig. 2). Glaucomatous damage increased in approximately half of the patients whose IOP was between 17 mm Hg and 21 mm Hg.

Following patients for a median period of 6 years with early glaucomatous visual field damage at study onset, Swedish investigators in the Early Manifest Glaucoma Trial (EMGT) reported a significantly lower rate of progression of perimetric damage in patients in whom IOP was reduced by a mean of 25% (5.1 mm Hg) with betaxolol drops and Argon laser trabeculoplasty (58/129; 45%) compared with those untreated (78/126; 62%).[15] Time to onset of such progression was delayed significantly—median 66 months in the treated group, versus a median 48 months in the observed cohort. For every 1 mm Hg drop in IOP, a 10% reduction in risk of glaucomatous progression was observed.

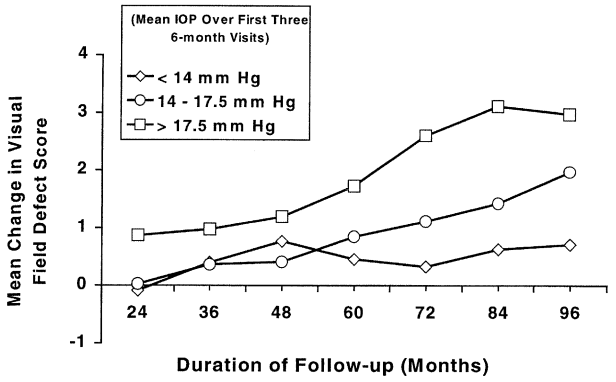

Fig. 1. Relationship between different levels of intraocular pressure and subsequent visual loss in a long-term study. In the Advanced Glaucoma Intervention Study, patients with mean intraocular pressures under 14 mm Hg over the first 18 months of follow-up exhibited the least change in visual field over up to 8 years of follow-up. (Reprinted from The AGIS Investigators[1] with permission of *American Journal of Ophthalmology.*)

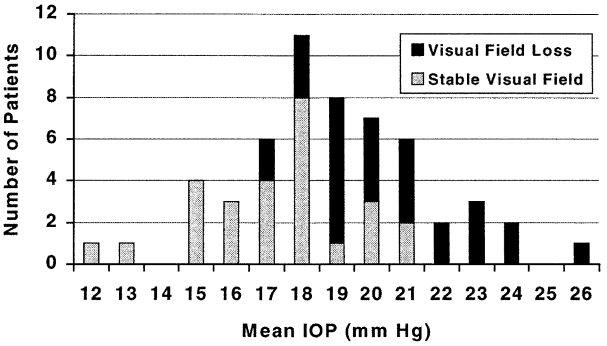

Fig. 2. Relationship between intraocular pressure control and subsequent visual loss in a long-term study. In 55 patients with early glaucomatous damage and intraocular pressure controlled either with drugs or trabeculoplasty, those with mean intraocular pressure below 17 mm Hg maintained stable vision over four to 11 years of follow-up. (Reprinted from Mao et al[16] with permission of *American Journal of Ophthalmology.*)

Even in glaucoma patients with IOP in the normal range (so-called normal-pressure glaucoma), reductions in IOP are beneficial in preserving the visual field. Involving 230 patients at 24 centers, the Collaborative Normal Tension Glaucoma Study Group (CNTG)[2] found that eyes that achieved and maintained at least a 30% reduction in IOP (mean IOP = 10.6 mm Hg) were significantly less likely than were untreated eyes (mean IOP = 16.0 mm Hg) to show progressive optic disk cupping or visual field defects or both (Kaplan–Meier survival analysis; $P < .0001$). Each normal-pressure glaucoma patient was randomized to IOP-lowering treatment (surgery and/or medication) or to no treatment. Follow-up examinations were scheduled every 3 months during year 1 and every 6 months thereafter for up to 8 years. IOP reduction by 30% reduced the risk of progressive visual field loss, even for glaucoma patients with normal IOP. The authors characterized normal pressure glaucoma as "either slowly or non-progressive." Eighty-eight percent of treated eyes (51/79) maintained their baseline visual field, compared with 65% of untreated eyes (54/61). However, there were factors besides IOP that contributed to visual field damage, since 12% of treated patients still developed further visual field loss, despite achieving IOPs 30% below baseline.

Lower IOP also prevents or delays the onset of visual field loss and optic disk damage in individuals with ocular hypertension (OHT), as was shown in the Ocular Hypertension Treatment Study (OHTS).[13] Eligible patients with no evidence of glaucomatous damage to optic discs or visual fields had an IOP between 24 mm Hg and 32 mm Hg in one eye, and between 21 mm Hg and 32 mm Hg in the other eye. The researchers randomized 819 participants to observation and 817 patients to topical glaucoma medication. Treated patients were set a target IOP of 24 mm Hg or less and a minimum reduction of 20% from baseline. After 60 months, the treated group achieved a 22.5% mean reduction in IOP, compared with a 4.0% reduction in the untreated group. The cumulative probability of developing primary open-angle glaucoma (POAG) was 4.4% in the treated group, compared with 9.5% in the observation group.

The Effect of a Low IOP Over Time on Vision Loss

The AGIS (7) study demonstrates the importance of maintaining a consistently low IOP over time (Fig. 3).[1] After surgery to reduce IOP, patients with IOP below 18 mm Hg at all visits on average suffered almost no visual field progression. During the 6-year follow-up, patients whose IOPs rose above 18 mm Hg even occasionally ($\leq$ 25% of all visits) experienced more visual field loss than those patients whose IOP remained below 18 mm Hg at all visits.

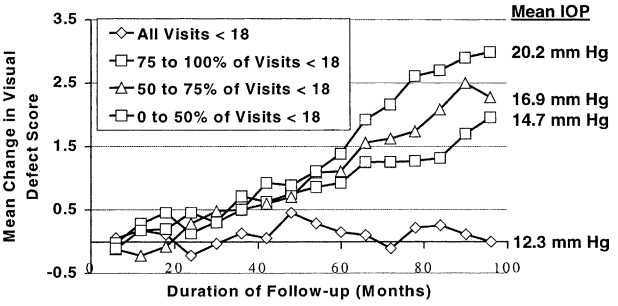

Fig. 3. Relationship between different levels of intraocular pressure and subsequent visual loss in a long-term study. This graph from the Advanced Glaucoma Intervention Study shows that only patients with intraocular pressures under 18 mm Hg at 100% of follow-up visits exhibited mean changes from baseline in visual field defect score close to zero. (Reprinted from The AGIS Investigators[1] with permission of *American Journal of Ophthalmology*.)

The Importance of a Steady IOP Throughout the Day and Night

IOP in individuals fluctuates throughout the day and night. Typically, IOP is lowest during the night, with a peak early in the morning. Large diurnal IOP fluctuations may be a significant risk factor for disease progression.[5,26] In a study of 64 glaucoma patients (105 eyes), those with wide diurnal IOP fluctuations were found to be at greater risk of visual field loss than those with more stable IOP levels throughout the day.[5] After 8 years of follow-up, 88% of patients in the upper quartile of diurnal IOP variability (range between highest and lowest IOP > 11.8 mm Hg) developed further visual defects, compared with 57% of patients in the lowest quartile (range < 7.7 mm Hg). Single IOP measures taken in the clinic did not predict the extent of diurnal variation as measured by trial participants using home tonometry. An additional finding was that a large variation in IOP over multiple days was also found to be a significant risk factor for progression of glaucomatous damage.

In an earlier study of 35 patients, Zeimer et al measured IOP using home tonometry five times daily over an average of 6.5 days. Patients who exhibited IOP peaks at home at least every second day, peaks that were at least 6 mm Hg higher than at the office, had a 75% probability of developing visual field loss.[26]

Because functional damage from high IOP is exponential, even transient elevations in IOP may cause significant glaucomatous damage. Patients who have periodic or sporadic pressure spikes can lose visual field due to cumulative effects.[10,20] An important goal of therapy, therefore, should be to prevent transient IOP elevations and achieve a low, stable IOP throughout the day and night. Unfortunately, the IOP that the clinician measures in the office only captures a

single moment and may not reflect the extremes of IOP that the patient experiences owing to fluctuations with the sleep/wake cycle or during different everyday activities. When evaluating the most at-risk patients, the clinician should attempt to measure IOP at several points during the day. If multiple diurnal measurements are not feasible, it is preferable to select therapies with more consistent 24-hour IOP control in clinical studies.

The Target Pressure Concept

With the relationship between IOP and glaucomatous visual loss clearly established, lowering IOP to an appropriate level reduces the risk of further visual loss. A "target" pressure should be set as a goal of long-term therapy: it should be chosen on an individual basis, weighing potential benefits and risks of treatment for each patient.

Because individuals vary in their susceptibility to IOP-dependent damage, there is no universal "safe" IOP that can be guaranteed to prevent further glaucomatous damage. The optic nerve that has already been damaged appears to be more susceptible to pressure-mediated injury, so patients with advanced glaucomatous neuropathy may require very low target pressures to halt the disease.[11,22] Patients with very severe or rapidly progressing disease can continue to deteriorate even though their IOP has been kept below 17 mm Hg. IOP in patients with advanced glaucoma should be reduced to target pressures under 15 mm Hg in order to prevent further visual field loss, as only those eyes with IOP $\leq$ 15 mm Hg had no further visual field loss over the15-year follow-up (Fig. 4).

How to Set a Target IOP

For a given patient, the target pressure should not be a single value; rather it should be a range of acceptable IOP levels within which the progression of glaucoma and visual field loss will be delayed or halted.[3] In determining an appropriate target pressure for an individual patient, the ophthalmologist must take into account several major factors: the IOP level at which optic nerve damage occurred;[23,27] the extent and rate of progression of glaucomatous damage, if known; the presence of other risk factors for glaucoma; and the patient's age, expected life span, and medical history. Of these four major factors, the first three determine the desirable therapeutic aggression needed, whereas the last one determines how reasonable it may be to treat the patient less ambitiously.

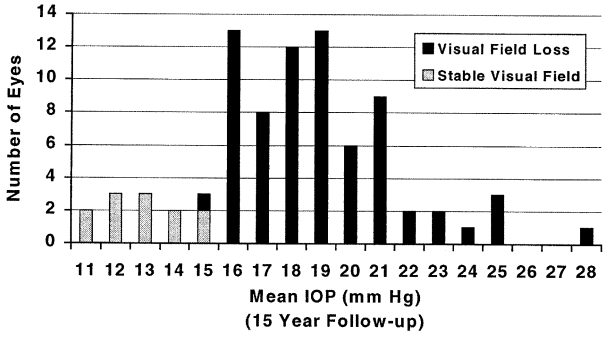

Fig. 4. Relationship between intraocular pressure and progression of visual field loss in advanced glaucoma. After 15 years of follow-up 85.5% of eyes developed progressive visual field loss. All 70 eyes with IOPs above 15 mm Hg developed further glaucomatous damage. Ten eyes with mean IOP $\leq$ 14 remained stable. (Reprinted from Shirakashi et al[22] with permission of *Ophthalmologica.*)

Although the clinician will not always know when optic nerve damage first occurred, the rate of progression can be measured by routine follow-up, provided accurate and appropriate baselines for disk structure and visual field sensitivities have been established. In addition, it is advisable to evaluate risk factors, such as diabetes,[14,17] cardiovascular disease,[4,12] sleep apnea,[18] and vasospastic syndromes[7] (e.g., migraine and Raynaud's phenomenon), as patients with multiple risk factors may progress more rapidly. Genetic risk factors refer particularly to a family history of glaucoma. Race also may be important, because blacks have been reported to be at greater risk for the development of glaucoma, and their disease is often more resistant to treatment.[3] However, an individual's particular family history is more predictive than this type of population-based generalization.

Specific IOP ranges may be recommended as a starting point. The American Academy of Ophthalmology guidelines suggest that for glaucoma patients with mild damage (optic disk cupping but no visual field loss), the initial target pressure should be 20–30% lower than baseline.[3] For patients with advanced damage, the target pressure range may be a reduction of 40% or more from baseline. In patients with normal pressure glaucoma, the initial target IOP should be a reduction from baseline of at least 30%. For those with open-angle glaucoma with IOP in the mid to high 20s, a reasonable initial target IOP could range from 14 mm Hg to 18 mm Hg. In cases of advanced glaucoma, the target should be established at less than 15 mm Hg. In a patient with OHT whose IOP is over 30 mm Hg with no sign of optic nerve damage, a target pressure in the low 20s with at least a 20% reduction from baseline may be acceptable.

A target IOP that is appropriate when you first see a patient may not be a safe pressure 10 years later when he or she may have developed systemic hypertension, diabetes, or some other condition that may affect the patient's susceptibility to glaucomatous progression. To determine if the target pressure originally chosen is still one that is most likely to protect the patient's vision, the clinician must reevaluate

each glaucoma patient at regular intervals. If appropriate baselines have been established, time can be used intelligently for the patient.

Summary and Recommendations

The evidence from the studies cited in this article is consistent: lower IOPs slow the development of glaucoma from OHT and slow the progression of glaucoma itself. The concept of a target IOP is a part of the standard of care for physicians who treat glaucoma patients. Individualized target IOPs should be set based on patient needs and reviewed periodically. In addition, treatment should strive to reduce IOP fluctuations during the day and night.

Patients with more severe disease need very low (< 15 mm Hg) IOPs to protect vision. The methods used to maintain the target pressure should be sustainable over the long term with minimal adverse effects.

Method of Literature Search

The author conducted a MEDLINE search in May 2002 using the search terms *glaucoma, ocular hypertension, and intraocular pressure*. He selected only those studies that he deemed to be the most relevant and rigorous.

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