

Treating Ocular Hypertension to Reduce Glaucoma Risk

When to Treat?

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Abstract

When to treat the patient who presents with ocular hypertension has been a question that has 'stumped' the ophthalmic community for decades. Population-based studies and intervention trials have provided the basis for understanding why we consider treating such patients. Although the EGPS (European Glaucoma Prevention Study) did not demonstrate that reducing intraocular pressure (IOP) with dorzolamide prevented the onset of glaucoma compared with individuals receiving a placebo, the investigators of the OHTS (Ocular Hypertension Treatment Study) found that the treatment of ocular hypertension can be delayed with topical medication when treated patients were compared with an observation group. There are differences in inclusion criteria, study design and retention rates between the EGPS and the OHTS, which may have led to the discrepancies in outcomes between these two studies. These differences provide a basis for understanding the relevance of the findings of both trials to clinical practice. The clinician should consider key risk factors such as age, thin corneal thickness measurements, large cup-to-disc ratio and mean IOP when determining who should be treated. However, the ultimate decision of when to treat will be determined by other issues such as life expectancy, the general health of the patient and the number of risk factors. Clearly, the treatment of only high-risk patients with ocular hypertension should be considered.

The question of who should be treated among ocular hypertensive patients is one that, until recently, has been difficult to answer. Most studies in the literature that predate the completion of the OHTS (Ocular Hypertension Treatment Study)^[1] were small, retrospective and differed in the way glaucoma was defined. Moreover, some studies determined that treatment is effective in slowing the conversion to glaucoma,^[2-6] while other studies demonstrated a lack of treatment effectiveness.^[7-12] Thus, there was no consensus in the literature that offered guidance to the clinician to determine who

should be treated. Ever since the publication of the EGPS (European Glaucoma Prevention Study),^[13] which failed to demonstrate the effectiveness of treatment of ocular hypertension, there may be questions raised by some clinicians regarding the value of treating these patients, who may be considered preglaucomatous. Therefore, before addressing the question posed by the title of this article, it is important to critically discuss the evidence that supports the treatment of 'high-risk' patients with ocular hypertension. Once the question 'Why should we

treat?' is addressed, we can then turn our attention to 'When we should treat?'

1. Why Should We Treat?

1.1 Consider the Prevalence of Ocular Hypertension and Primary Open Angle Glaucoma

It is difficult to assess the prevalence of ocular hypertension, given the variation that exists in the literature with regard to its definition. In a population of Australians, the prevalence of ocular hypertension was estimated to be 5% of individuals 50 years and older.^[14] In another population study, which included primarily Mexican-Americans, it was noted that 3.56% of individuals in the study had ocular hypertension. Older participants (aged ≥ 80 years) were three times more likely to have ocular hypertension than younger individuals (aged 40–49 years).^[15] This finding is similar to other studies which noted an age-related increased prevalence of ocular hypertension. In the Beaver Dam Study, the prevalence of ocular hypertension ranged from 2.3% among those 43–49 years of age to 7.7%, among those individuals 75–79 years of age.^[16] The Latino Eye Study determined that as many as 75% of individuals with either ocular hypertension or glaucoma were undiagnosed prior to entering the study.^[15] In fact, glaucoma is considered the second leading cause of blindness worldwide^[17] and, unfortunately, a significant proportion of at-risk patients remain either undiagnosed, untreated or undertreated.

In the US, the prevalence of primary open angle glaucoma (POAG) has been estimated to be 1.86% (95% CI 1.75, 1.96), which converts to approximately 2.22 million individuals. By the year 2020 it is predicted that the number of individuals affected with glaucoma will increase by 50%.^[18] The prevalence of visual impairment among individuals with open angle glaucoma was noted to be 6.6% in the Latino Eye Study.^[15] Although this proportion may be considered small, it is significantly greater than the prevalence of visual impairment among those individuals without the diagnosis of open angle

glaucoma, which was 1.07%. Thus, from a public health standpoint it is important to identify those individuals at risk of developing open angle glaucoma at an early stage when treatment may be more effective in halting the disease process.

2. What is the Evidence that Treatment of Ocular Hypertension is Effective?

Recently, the investigators involved in the EGPS published the results of their 5-year study. In the EGPS, patients with ocular hypertension were randomised to either treatment with dorzolamide 2% three times daily or placebo three times daily. Interestingly, the investigators failed to demonstrate any statistical difference between the treated and control groups, suggesting a lack of benefit for treating individuals with ocular hypertension.^[13] Taken in isolation, such a finding would place the entire premise of this article in question, as there would be no indication to even consider treating patients with ocular hypertension. However, a close analysis of this study, the OHTS and a review of an analysis of relevant population-based studies^[19] should reaffirm the validity of considering the question regarding which individuals with ocular hypertension should be treated.

The EGPS sought to evaluate the efficacy and safety of reducing intraocular pressure (IOP) with dorzolamide 2% in hypertensive eyes. Patients included in the study were between 30 and 80 years of age, had an IOP of at least 22mm Hg but no higher than 29mm Hg in at least one eye, two normal and reliable visual fields, and open angles. Patients were excluded if their visual acuity was $<20/40$ in both eyes, had undergone previous intraocular surgery or who had evidence of diabetic retinopathy, that may have an affect on either the visual field or optic disc. Following randomisation, patients were followed with visual fields and stereo disc photography every 6 months. Only one eye of a participant could be entered into the study. Interestingly, the mean percentage reduction in IOP from baseline ranged from 14.5% at 6 months to 22.1% at 5 years versus a range of 9.3% for the placebo at 6 months to 18.7% at 5 years. After 5 years, the cumulative probability

of converting to glaucoma was 13.4% in the dorzolamide group and 14.1% in the placebo group ($p = 0.45$).^[13]

On the other hand, the OHTS, which randomised patients with ocular hypertension to either treatment or no treatment, found a beneficial effect of treatment. Following randomisation, eligible patients were followed with perimetry every 6 months and stereo disc photography annually. After 60 months of follow-up, the cumulative probability of developing glaucoma was 4.4% in the treated group versus 9.5% in the observation group ($p < 0.0001$).^[1]

So, what are the possible differences between these two well conducted clinical trials which may have led to the discrepancies in the results? First of all, it is important to examine the differences in study design. In the OHTS, the investigators were asked to set a minimum goal of 20% reduction from baseline and, in fact, 87% of patients achieved this goal in both eyes. Also, it is important to note that as many as 40% of patients in the OHTS required more than one medication to achieve this goal.^[1] In contrast, investigators were asked to adhere to a strict regimen in the EGPS and a specific target reduction in IOP was not required. Although a 22% reduction in IOP was achieved in 60 months in the dorzolamide group, the comparable number in the placebo group was 18.7%.^[13] In the OHTS, the reduction in IOP over time varied only 4% below baseline in the observation group.^[1] Whether the marked reduction in IOP in the EGPS placebo-treated group was related to the composition of the placebo, or if the topical agents may have been confused between study arms is unclear. Nevertheless, the use of a placebo adds another element of difference between the OHTS and the EGPS.

The inclusion criteria were quite different between the two studies. In the EGPS, patients as young as 30 years of age were allowed in the study.^[13] On the other hand, a higher threshold of 40 years of age was used in the OHTS.^[1] This difference raises two issues. First, the inclusion of individuals in the third decade introduces the chance that patients with either juvenile onset primary open angle glaucoma or pigmentary glaucoma may be

included. The natural history of these patients may be different compared with others at risk of developing primary open angle glaucoma. Secondly, overall, younger patients may be at lower risk than older patients. Nevertheless, since both studies were randomised, such a difference may not be significant. However, the inclusion of one eye of an individual with ocular hypertension in the EGPS does raise a concern. Such eyes will be subjected to the effects of treatment in the fellow eye, particularly if these fellow eyes were treated with a β -adrenoreceptor antagonist (β -blocker).^[20]

There are two other points that are worthy of discussion when comparing the OHTS^[1] and the EGPS:^[13] (a) the retention rate throughout the study; and (b) the assessment of the optic discs. Although at 5 years, the percentage reduction in the treated group of the EGPS was 22%, it is difficult to assess this finding given that retention was only 64.4% in the dorzolamide group. The placebo group was not much higher at 75.3%. In the OHTS, the retention rate at 5 years was 86.6% for self-reported African American participants and 91.4% for others. The high withdrawal rate in the EGPS may have critically affected the outcome of this study. It may be that those who left the EGPS did so with higher IOP measurements and thus the reduction of 14.5% may be closer to the true reduction since a greater proportion of treated patients were still in the study at 6 months. The assessment of the optic nerve should also be considered. In the OHTS, a confirmatory optic disc photograph was performed once there was the suggestion of progression.^[1] In the EGPS, such a confirmatory photograph was not done, which may have contributed to a higher than desired number of false positives.^[13] These differences between the OHTS and the EGPS are summarised in table I, and are offered as mere suggestions when assessing the results of these two major studies.

Using data from population-based studies^[21-23] and randomised, multicentre, interventional clinical trials,^[24-26] Weinreb and colleagues^[19] estimated the risk of progression among individuals with treated and untreated ocular hypertension and 'the number-needed-to-treat' (NNT), a number derived by calcu-

Table 1. Characteristics of the European Glaucoma Prevention Study that may have impacted on the results

Characteristics	Impact
Rigid regimen requiring the use of either tid medication or placebo	Inadequate IOP reduction
Use of a placebo in one arm	Potential confusion of agents between arms or direct effect of placebo on IOP
Inclusion of eyes rather than patients	Crossover effect of drugs used in the non-study fellow eye
Inclusion of younger patients	Inclusion of patients at lower risk
IOP reduction <20% at 6mo	Inadequate IOP reduction to result in any therapeutic effect
Poor retention of patients	Negative impact on the sample size

IOP = intraocular pressure; **tid** = three times daily.

lating the inverse of the difference in absolute risk between control and treatment groups. This number essentially reflects the ability of a treatment to prevent a specific outcome, such as unilateral blindness that would have occurred if treatment had not been initiated. Among the untreated patients, Weinreb and colleagues^[19] estimated the risk of an individual with ocular hypertension progressing to monocular blindness to be from 1.5–10.5% versus 0.3–2.4% among treated individuals over a 15-year period. Consequently, the NNT is anywhere from 12 to 83 patients. In other words, this range represents the NNT before one could prevent monocular blindness in one patient. Basing their analysis solely on the OHTS, Coleman and colleagues^[27] estimated the NNT to prevent progression to glaucoma to be 20 over a 5-year period. Taking this analysis one step further and applying a higher threshold of 26mm Hg versus 24mm Hg for determining who should be treated, Kumar and colleagues^[28] estimate the NNT to be 6. Thus, it appears that when one considers the large body of evidence, treatment of ocular hypertension is effective. However, by limiting the treatment to those who may be at higher risk of developing glaucoma, the treatment may be considered more cost effective.

3. Who Should Be Treated Among Ocular Hypertensive Patients?

Friedman and co-workers^[29] performed a critical review of the literature and determined key risk factors that should be considered when determining who among ocular hypertensive patients should be treated. In this analysis, important risk factors included older age, higher IOP, greater cup-to-disk ratio and thin corneal thickness measurements. In the past, ethnicity would have been included on this list. However, when one considers the analysis of the 408 self-reported African American patients in the OHTS, ethnicity did not prove to be a risk factor since most individuals in this group showed large cup-to-disc ratios and thin corneae.^[30] Greater pattern standard deviation at baseline also proved to be significant in the multivariate analysis of baseline factors in the OHTS.^[31] However, since this parameter is based on an average of several visual fields, it is not as clinically useful as other risk factors. Recently, investigators of the OHTS and EGPS compared the hazard ratios (HR; univariate) of the baseline factors of patients enrolled in the observation group (OHTS) and the placebo group (EGPS). They found the ratios to be generally similar.^[32] This finding underscores the robust nature of the risk factors noted below.

3.1 Mean Intraocular Pressure

Although mean IOP did not prove to be as significant in the OHTS^[1] as other risk factors, such as thin central corneal thickness measurement, this parameter should be strongly considered when determining who should be treated. In the OHTS, the risk was more than double when one accounted for those individuals who progressed and had a mean baseline IOP of 22.2mm Hg and central corneal thickness (CCT) $\leq 555\mu\text{m}$ versus a mean IOP of 27.9mm Hg and CCT $\leq 555\mu\text{m}$. When considering mean follow-up IOP, both the OHTS and the EMGTS (Early Manifest Glaucoma Treatment Study), which randomised newly diagnosed glaucoma patients to either treatment or no treatment,^[26] noted an increased risk of 10% for every 1mm Hg in IOP.

Diurnal IOP fluctuation and asymmetry of IOP may also be important.^[33,34]

3.2 Greater Cup-to-Disc Ratio

In the OHTS,^[1] both horizontal (HR, multivariate, 1.27; 95% CI 1.14, 1.40) and vertical (HR, multivariate, 1.32; 95% CI 1.19, 1.47) cup-to-disc ratio proved to be important risk factors. Since large cup-to-disc ratio is related to disc area, it will be interesting to determine if disc area will prove to be more important once additional data are released from the OHTS.

3.3 Thin Central Corneal Thickness

Probably the greatest surprise from the OHTS data was the strong influence of central corneal thickness. Although recognised as an artifact of Goldman applanation tonometry,^[31] the persistence and the magnitude of the CCT in the multivariate analysis of baseline factors was quite remarkable (HR 1.71; 95% CI 1.40, 2.09 per 40µm thinner).^[1] Thus, when considering patients with ocular hypertension, central corneal thickness measuring <555µm should be strongly considered in the decision to treat.

3.4 Older Age

It is well known that the risk of glaucoma increases with increasing age and, certainly in the OHTS, age was noted to be a significant risk factor (HR, multivariate, 1.22; 95% CI 1.01, 1.49).^[1] Other prospective, multicentre, interventional studies involving patients with primary open angle glaucoma have demonstrated a significant contribution of age to the progression of disease.^[24,25,35]

3.5 Other Factors

Although the four factors highlighted in sections 3.1 to 3.4 should be considered the primary risk factors for determining who should be treated, there are other points that should be noted. Family history, the status of the fellow eye, disc haemorrhage and evidence of exfoliation should be considered.^[29] Diabetes mellitus may be important, although the evi-

dence for this chronic disease as a risk factor is not strong in the literature. However, in both the AGIS (Advanced Glaucoma Intervention Study)^[24] and the EMGTS,^[26] the presence of diabetes was associated with a greater likelihood of progressive glaucoma.

4. When Should One Treat?

Not everyone with ocular hypertension should be treated. It is important for the clinician, in consultation with the patient, to weigh the combination of risk factors, life expectancy of the patient, presence of other co-morbidities, and the patient's understanding and acceptance of his or her status as someone likely to develop glaucoma. The impact of the presence of a combination of risk factors is best reflected in the analysis of self-reported African Americans in the OHTS. Most individuals in this cohort had both thin corneal measurements and large cup-to-disc ratios. Consequently, the rate of conversion to glaucoma was higher in this group in both the treated (8.4% vs 4.4% overall) and untreated (16.1% vs 9.5% overall) groups.^[30] Table II summarises the key risk factors to consider when making a clinical therapeutic decision.

Consider the following scenarios. A 75-year-old patient with a small cup-to-disc ratio and an IOP in the mid 20s may be a candidate for observation, while a 40-year-old individual with an IOP in the mid 20s and a corneal thickness of 500µm may be a candidate for treatment. The latter patient should be treated in preference to the former patient who only has two risk factors and a more limited life expectancy. Given that at least 90% of patients with ocular hypertension will not go blind in one eye from glaucoma over a 15-year period, it is important to

Table II. Key risk factors for glaucoma to consider in patients with ocular hypertension

Thin central corneal thickness measurement
Large cup-to-disc ratio
Older age
Higher mean IOP
Other factors: IOP fluctuation, disc haemorrhage, family history of blindness, status of the fellow eye, exfoliation
IOP = intraocular pressure.

carefully weigh the cost and inconvenience of treatment against the quality of life of the individual. The critical task is to determine if the individual who faces you in your office is likely to fall within the 10% of individuals who will indeed progress to glaucoma. If one considers close observation as a 'form of treatment,' then the decision to simply observe even those patients who are at moderate risk can be a rational approach for the well informed patient. Once the additional data are available from continued follow-up of patients registered in well conducted long-term studies, then we may apply greater precision when determining when and in whom ocular hypertension should be treated. Until then, clinicians must rely on their own clinical judgment and careful assessment of key risk factors, and should involve patients in a detailed discussion regarding their options.

5. Conclusions

When to treat individuals with ocular hypertension has been a longstanding question among clinicians. Two studies, the OHTS and the EGPS, both large randomised, multicentre clinical trials, have evaluated this question among patients with ocular hypertension. However, differences in study design and the inclusion criteria as well as a significant loss of patients in the EGPS led to critical differences in the outcome of these two studies. The OHTS demonstrated that high-risk patients with ocular hypertension do benefit by having their intraocular pressure reduced with topical therapy; however, the EGPS failed to demonstrate such a benefit. Nevertheless, considering the ultimate risk of blindness that may occur when specific patients remain untreated, the identification of key risk factors such as higher IOP, greater cup-to-disc ratio, thin central corneal thickness and older age are important to consider when formulating a treatment plan for any given patient. Since most individuals with ocular hypertension will not progress to glaucoma, clinicians should carefully consider these specific risk factors and other factors such as life expectancy before committing a patient to a lifetime of treatment.

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