Eye (2007) 21, S51–S54

www.nature.com/eye

A clinical trial studying neuroprotection in low-pressure glaucoma

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Abstract

The Low-Pressure Glaucoma Treatment Study is a double-masked, randomized trial comparing the visual outcomes of 190 low-pressure glaucoma patients randomized to intraocular pressure reduction with brimonidine tartrate or timolol maleate. Baseline characteristics of participants are compared to published studies.
Eye (2007) **21,** S51–S54; doi:10.1038/sj.eye.6702890

Keywords: low-pressure (tension) glaucoma; neuroprotection; brimonidine; clinical trial; visual field loss; central corneal thickness

Introduction

Open-angle glaucoma is a family of disorders characterized by a slow progressive neurodegeneration of retinal ganglion cells and their axons[1] with degenerative changes along the retinogeniculocortical pathway.[2] Normal-tension glaucoma is a type of open-angle glaucoma that occurs with an untreated intraocular pressure (IOP) in the statistically normal range, usually $\leqslant$21 mmHg. My personal preference is to use the term 'low-pressure glaucoma' (LPG), rather than 'normal-tension glaucoma'. Use of the term 'normal' in this condition relates to statistically normal, not pathologically normal. It is awkward to use 'normal' when discussing the disease with a patient who is worried about blindness, and the only 'tension' involved is that experienced by the patient and the ophthalmologist in facing this disease.

Low-pressure and high-pressure open-angle glaucoma are a continuum and cannot be separated by a single IOP level. The degree of IOP is the most important risk responsible for disease progression and the only factor amenable for change. Several clinical trials have confirmed the value of decreasing IOP in patients with ocular hypertension,[3,4] high-pressure open-angle glaucoma,[5–7] and LPG.[7–9] However, decreasing IOP does not necessarily halt the glaucomatous process.

Basic biological research over the past decade has been directed to mechanisms and treatments that underlie chronic neurodegenerative disorders, including glaucoma,[10] such as the steps of neuronal apoptosis including responses to excitatory neurotransmitters, regulation of ion channel activities, and modulation of signal transduction pathways.

Neuroprotection is a therapeutic strategy directed at keeping retinal ganglion cells alive and functionally connected to their targets in the brain. α_2-Adrenergic agonists have a neuroprotective effect in animal models of focal cerebral ischaemia.[11] Systemic administration of brimonidine (Alphagan, Allergan Inc., Irvine, CA, USA), a selective α_2-adrenergic agonist, has been shown to protect the optic nerve and retinal ganglion cells from secondary degeneration following a partial crush injury to the adult rat optic nerve[12] and to protect retinal ganglion cells in the ocular hypertensive rat model.[13] Possible molecular mechanisms for brimonidine's neuroprotective effect relates to upregulation of neuronal survival factors, brain-derived neurotrophic factor mRNA expression in retinal ganglion cells,[14] and basic fibroblast growth factor mRNA expression in the retina.[15]

Neuroprotective activity must be demonstrated in randomized controlled clinical trials, which was the purpose of the Low-pressure Glaucoma Treatment Study (LoGTS). This paper reviews LoGTS study design and descriptions of the baseline patient characteristics.[16]

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Study design

LoGTS is a multicentre, prospective, randomized, double-masked, two-arm parallel group study comparing the efficacy of brimonidine 0.2% *vs* timolol 0.5% to alter the course of LPG as measured by the rate of visual field progression. Study investigators are listed in Table 1.

Subjects included 190 men and women, $\geqslant$30 years of age, with previously diagnosed LPG in at least one eye and untreated IOP of $\leqslant$21 mmHg on a diurnal pressure curve on day zero. The diagnosis of LPG required open iridocorneal angles by gonioscopy and glaucomatous visual field defects in at least one eye on Humphrey 24-2 full-threshold standard automatic perimetry. At least two visual field examinations with acceptable reliability standards were required within the prior 6 months. Vision of at least 20/40 was also required.

Pertinent exclusion criteria included a history of treated or untreated IOP greater than 21 mmHg and an untreated IOP greater than 21 mmHg during a pre-randomization diurnal curve. Patients with advanced glaucoma (mean deviation $>$15 decibels) were excluded, as well as those with evidence of exfoliation, pigment dispersion, or prior filtration surgery.

The primary end point was visual field. Patients were examined at 1 and 4 months after initiation of treatment randomization and every 4 months thereafter. Baseline visual field was defined as the average of two pre-randomization examinations. Optic discs were evaluated by physician assessment every 4 months and by photographs at baseline and every year thereafter. Photographs were evaluated at the Optic Disc Reading Center. Central corneal thickness (CCT) was measured.

Table 1 Low-pressure glaucoma study group investigators

University Eye Specialists, Chicago, IL, USA
Theodore Krupin, MD, Lisa F Rosenberg, MD, Jon M Ruderman, MD, John W Yang, MD

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Wills Eye Hospital, Philadelphia, PA, USA
Jonathan S Myers, MD, L Jay Katz, MD, George L Spaeth, MD, Douglas J Rhee, MD, Richard P Wilson, MD, Marlene R Moster, MD

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Ronald L Gross, MD

Rapid City, SD, USA
Monte S Dirks, MD

Brooke Army Medical Center, San Antonio, TX, USA
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Bascom Palmer Eye Institute, University of Miami School of Medicine, Palm Beach Gardens, FL, USA
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Little Rock Eye Clinic, Little Rock, AR, USA
J Charles Henry, MD

Wheaton Eye Clinic, Wheaton, IL, USA
David K Gieser, MD

Scheie Eye Institute, University of Pennsylvania, Philadelphia, PA, USA
Jody R Piltz-Seymour, MD

Age

The average patient age was 64.9 $\pm$ 10.7 years (mean $\pm$ SD). Twenty-two patients (11.6%) were younger than 50 years of age. The Beaver Dam Eye Study[17] had shown earlier that the prevalence of LPG increased with age, from 0.2% in the 43–54 age group to 1.6% in the over 75 age group, with 63.6% of the patients older than 64 years. In the LoGTS, only 54.2% of patients were older than 64, a smaller percentage than the Beaver Dam Study. This may relate to improved clinical evaluation of the optic nerve. The incidence of LPG at younger ages will surely increase as more attention is placed on evaluation of the optic nerve during routine eye examinations.

Sex

There were more women (n = 113; 59.5%) than men (n = 77; 40.5%; P = 0.0003). Earlier reports on gender distribution of LPG have reported greater frequency in women,[18,19] greater frequency in men,[20] or an equal distribution between the sexes.[17]

Family history

In the LoGTS, 30% of the patients had a family history of chronic open-angle glaucoma, and a 4% had a family history of LPG.

Migraine

Phelps *et al*[21] reported a 37% incidence of migraine in LPG patients, higher than in normal subjects or COAG

patients by about 22%. A history of migraine headaches was reported in nine participants (4.7%), a finding similar to earlier findings in the Beaver Dam Study[17] and a study by Lewis *et al*.[22]

Vasospasm

Although previous reports have cited a high occurrence of functional peripheral vasospasm (up to about 65%),[20,23] only 16 LoGTS participants (8.4%) reported a history compatible with Raynaud's phenomenon.

Visual field loss

Visual field defects in both eyes were present in 137 patients (72.1%); unilateral defects were present in 53 patients (27.9%) at baseline, with the left eye more commonly involved (56.6%). This was similar to the 25% occurrence of unilateral field loss (64% left eye) in LPG reported by Poinoosawmy *et al*.[24]

The unilateral field loss patients were younger than those with bilateral defects, with the proportion of unilateral cases decreasing with increasing age (Figure 1). The younger age of these patients may relate to earlier detection of optic nerve damage in those with a normal IOP.

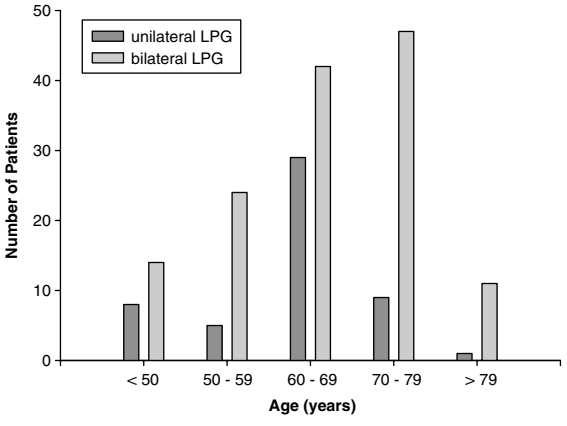

Figure 1 Age distribution for bilateral ($N=137$) and unilateral ($N=53$) visual field defects at baseline in the Low-Pressure Glaucoma Treatment Study (LoGTS) subjects.

Cupping

As expected, cup-to-disc ratios in the unilateral field loss participants were higher ($P<0.0001$) in the eyes with field loss (0.75 ± 0.12) than in the fellow eyes without visual field damage (0.60 ± 0.17).

Optic disc haemorrhage

Evaluation of baseline optic disc photographs was performed by three observers for the presence of a disc haemorrhage defined as adjacent to or touching the disc edge and within the rim tissue. A haemorrhage was present in 29 patients (32 eyes).

IOP

The mean of the four baseline diurnal readings of nontreated IOP was equal in both eyes (Table 2). There was no difference between eyes in the mean nontreated diurnal IOP of the 137 bilateral field loss patients. There were 18 bilateral patients who had some asymmetry in pressure. Nontreated diurnal IOP was similar between the eyes of the 53 unilateral field loss subjects. Most eyes were equal in IOP by 1 mmHg, although there were 12 subjects who had higher pressure in the field loss eye and eight subjects who had lower pressure in the field loss eye.

Corneal thickness

CCT (microns) was measured in 168 of 171 phakic patients. Mean CCT was 543 ± 35 with a range from 435 to 655. CCT was less than 500 in 15 patients (30 eyes; 8.9%) and more than 600 in 11 patients (22 eyes; 7.1%). There was no statistically significant difference in CCT between the bilateral field loss patients and the unilateral field loss patients. The impact of corneal thickness obviously is that thin CCTs can underestimate the true IOP and can classify a patient inaccurately as having LPG

Table 2 Baseline diurnal intraocular pressure measurements

Time	*Right eyes (mmHg)*[a]	*Left eyes (mmHg)*[a]
0800 hours	15.9 ± 2.8 (10.0–21.0; 15.5, 16.3)	16.0 ± 2.7 (8.0–20.5; 15.7, 16.3)
1000 hours	15.5 ± 2.7 (9.5–20.5; 15.1, 15.9)	15.6 ± 2.8 (7.5–21.0; 15.2, 16.)
1200 hours	15.5 ± 2.6 (8.0–20.5; 15.1, 15.9)	15.6 ± 2.6 (8.0–20.5; 15.2, 15.9)
1600 hours	14.9 ± 2.8 (8.5–20.0; 14.9, 15.7)	15.4 ± 2.8 (8.0–20.5; 15.0, 15.8)

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[a]Mean $\pm$ SD (range; 95% confidence intervals).

(IOP less than 22 mmHg in our study). Shah *et al*[25] have reported low mean CCTs in 52 of 514 patients with low-pressure glaucoma. The LoGTS does not confirm an excess of thin corneas in LPG patients.

Summary

The baseline characteristics of the large group of LPG patients enrolled in the prospective LoGTS clinical trial provide useful information on IOP, visual field loss, and optic nerve haemorrhages. These data can help in formulating better treatment paradigms for open-angle glaucoma patients with relatively low IOPs.

Acknowledgements

This study was supported by an unrestricted grant to the Low-pressure Glaucoma Study Group from Allergan Inc., Irvine, CA, USA and the Chicago Center for Vision Research, Chicago, IL, USA. The author has no financial interests in the drugs or devices described in this article.

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