

## A randomized trial of brimonidine versus timolol in preserving visual function: results from the low-pressure glaucoma treatment study

### Background:

- The pathophysiologic mechanisms by which glaucomatous neurodegeneration occurs are not completely understood, and elevated intraocular pressure (IOP) is the most important known risk factor for disease progression that is amenable to treatment. However, disease progression is still seen in patients with reduced IOP.
- Knowing this, it is important to evaluate glaucoma treatments with regard to visual field progression as opposed to strictly IOP reduction.

### Objective:

- To compare the  $\alpha$ 2-adrenergic agonist brimonidine tartrate 0.2% to the  $\beta$ -adrenergic antagonist timolol maleate 0.5% in preserving visual function in low-pressure glaucoma.

### Methods:

- **Design:** Four year, multicenter, double blinded, stratified randomized, active control clinical trial.
- **Inclusion criteria:** previously diagnosed low-pressure glaucoma that fulfilled the following eligibility criteria: had untreated IOP  $\leq$  21 mmHg, open iridocorneal angles, 2 reproducible visual fields with glaucomatous defects in one or both eyes with the location of the field defect consistent with the photographic appearance of the optic nerve head, and are 20 years old or older.
- **Exclusion criteria:** IOP  $>$  21 mmHg, best-corrected visual acuity worse than 20/40 in either eye, a history of angle closure or an occludable angle by gonioscopy, prior glaucoma incisional surgery, inflammatory eye disease, prior ocular trauma, diabetic retinopathy or other diseases capable of causing visual field loss or optic nerve deterioration, extensive glaucomatous visual field damage with a mean deviation worse than negative 16 dB, or a clinically determined threat to central fixation in either eye. Systemic exclusion criteria include: HR  $<$  50 BPM, severe or uncontrolled DV, renal or pulmonary disease, MI, or stroke.
- **Primary outcome measure:** Visual field progression in either eye, defined as the same 3 or more points with a negative slope  $\leq$  -1dB/year, on 3 consecutive tests, assessed by pointwise linear regression (power = 80%).
- **Secondary outcome measures:** Visual field progression in either eye, evaluated by Humphrey glaucoma change probability maps (GCPM), and using a 3-omitting method for pointwise linear regression.
- **Enrollment:** 178 patients were enrolled into two treatment arms:
  - 99 in the brimonidine tartrate 0.2% treatment group
  - 79 in the timolol tartrate 0.5% treatment group
    - Both medications were administered twice daily to both eyes
- **Data handling method:** Data were handled with the intent to treat principle.

### Results:

- 99 patients completed the study.
  - 54 in the timolol group
  - 45 in the brimonidine group

- **Primary outcome measure:** A visual field endpoint was reached in significantly fewer brimonidine patients than timolol patients (9 and 31 respectively, p-value 0.001).
- **Secondary outcome measures:** Visual field progression was statistically (p-value 0.001) less in brimonidine patients than timolol patients (8 and 35 respectively) by GCPM, and likewise by the 3-omitting method (5 in brimonidine, 21 in timolol, p-value 0.002).
- **Author's conclusion:** Twice daily topical brimonidine 0.2% preserves visual field better than twice daily topical timolol 0.5% in a subset of open-angle glaucoma patients with statistically normal IOP.

**Strengths:**

- The type of study performed is the gold standard for an active comparator study.
- The use of multiple tests to assess visual field progression.
- Specific and appropriate inclusion/exclusion criteria.

**Limitations:**

- Small sample size/high drop-out rates
- Did not follow dropouts
- Additional measurements (various IOP's) could have ruled out potential mechanisms of action providing brimonidine benefit.

**Conclusion:**

- Further study is needed to fairly evaluate brimonidine's efficacy versus timolol in low-pressure glaucoma patients. Although the results reported were statistically and potentially clinically significant, the high rates of drop out could have skewed these results. Additionally, further study needs to be conducted to rule out some of the potential advantageous mechanisms of action to determine what, if any, benefit brimonidine offers other than IOP reduction.

**Reference:** Krupin T, et al. A randomized trial of brimonidine versus timolol in preserving visual function: results from the low-pressure glaucoma treatment study. Am J Ophthalmol. 2011;151(4):671-81.

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