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Effect of brimonidine on intraocular pressure in normal tension glaucoma: A short term clinical trial

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PURPOSE. *To evaluate the efficacy and safety of 0.2% brimonidine eye drops given twice daily in normal tension glaucoma.*

PATIENTS AND METHODS. *Sixteen consecutive patients fulfilling eligibility criteria (glaucomatous optic neuropathy associated with visual field defect in at least one eye, intraocular pressure (IOP) ≤ 18 mmHg (average of the two highest readings of the round-the-clock curve, including one reading at midnight in supine position), no prior glaucoma therapy, angle wide open, visual acuity 20/40 or better) were enrolled in this prospective, randomized, placebo-controlled clinical trial with crossover design, lasting 30 days for each treatment phase plus 15-day washout in between. Main outcome was IOP (average of the two highest readings of the round-the-clock curve).*

RESULTS. *Mean IOP was significantly reduced by brimonidine (from 17.1 ± 0.7 mm Hg to 13.9 ± 2.2 mmHg, p<0.001 (paired Student t-test)). At the end of the 30-day brimonidine phase, 4 of 16 subjects showed a ≥30% IOP decrease over baseline.*

CONCLUSIONS. *In the short term, 0.2% brimonidine eye drops can induce a significant IOP decrease in eyes with normal tension glaucoma. (Eur J Ophthalmol 2003; 13: 611-5)*

KEY WORDS. *Normal tension glaucoma, Brimonidine, Target IOP*

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INTRODUCTION

The treatment of normal tension glaucoma is a matter of discussion. Recently, two prospective trials suggested that low tension glaucoma might benefit in the long term from intraocular pressure (IOP) reduction, obtained by either medical or surgical treatment (1, 2).

Brimonidine tartrate, an alpha-2 selective agonist, provides long-term ocular hypotensive efficacy comparable to that of timolol 0.5% twice daily in eyes with ocular hypertension or high tension primary open angle glaucoma (3-5). However, no data are available to establish any possible role of brimonidine as a pressure-reducing agent in glaucomatous eyes showing a baseline IOP within the normal limits (i.e., low tension glaucoma). This clinical trial was designed to address this issue.

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PATIENTS AND METHODS

Sixteen consecutive patients referred to the Glaucoma Research and Care Center of our University and meeting eligibility criteria were enrolled in this prospective, investigator-masked, randomized, placebo-controlled, crossover clinical trial.

Eligibility criteria

The eligibility criteria were as follows:

- Glaucomatous optic neuropathy in at least one eye (assessed by slit lamp indirect ophthalmoscopy), combined with visual field defect (24/2, full threshold, Humphrey Field Analyzer, Dublin, CA)
- IOP ≤ 18 mm Hg (average of the two highest readings of the round-the-clock curve), measured by Goldmann applanation tonometry in the sitting position, and by Perkins hand-held portable applanation tonometer in supine position (one reading at midnight)
- Best-corrected visual acuity >20/40 (Early Treatment Diabetic Retinopathy Study Chart)
- Angle wide open with normal pigmentation and no malformation detectable on routine dynamic gonioscopy
- No iris abnormalities
- No prior glaucoma therapy
- No prior bulbar surgery.

Upon enrollment, each patient gave informed consent to participate in the study. Then the patients were randomly allocated to either brimonidine tartrate 0.2% twice daily or artificial tears in affected eyes for 30 days. In bilateral cases, both eyes were allocated to the same treatment, but the left eye only was arbitrarily considered for analysis (16 eyes). IOP was measured on day 1 and day 30 on a round-the-clock inpatient basis. Eight readings were performed at the following time points: 8:00 am (trough), 10:00 am (peak), 12:00 am, 2:00 pm, 4:00 pm, 6:00 pm, 9:00 pm, and midnight (in supine position). During the treatment phase, the scheduled drug (i.e., either brimonidine or artificial tears) was self-administered by the patient under the supervision of an observer, 10 to 15 minutes after the 8 am IOP reading and at 8 pm. The average of the two highest readings was considered for analysis. A paired-sample Student t-test was further applied on the mean IOP diurnal readings for each time-point of the round-the-clock profile.

At the end of this first phase, each patient had a 15-day washout. A new assessment of the IOP was performed before the subjects entered the opposite treatment. IOP was then measured on day 1 and day 30, following the above detailed experimental setting.

Systemic and topical adverse events were monitored through questioning the patients and through slit-lamp examination. For safety reasons, best-corrected visual acuity (logMar) was assessed at recruitment and at the end of each treatment phase.

Data were analyzed on an intent-to-treat basis. Paired Student t-test was adopted when comparing means.

RESULTS

Each patient completed the study; the demographics are detailed in Table I.

Table II summarizes the adverse events recorded through the different phases of the crossover. Visual acuity did not change significantly during the study

TABLE I - DEMOGRAPHICS OF THE 16 PATIENTS ENROLLED

Characteristics	Values
Age, years, mean ± SD	61 ± 10
Sex, F/M	6/10
IOP, mmHg, mean of every reading ± SD	15.6 ± 1.57
IOP, mmHg, median of every reading	16
Refraction, diopters, mean ± SD	-0.75 ± 2.25
Visual acuity, logMar, mean ± SD	0.14 ± 0.16
Mean defect, dB, mean ± SD	11.74 ± 5.42
Corrected pattern standard deviation, mean ± SD	13.42 ± 7.36
History of cardiovascular disease, %	68.7
Prior therapy with insulin, %	18.7

SD = Standard deviation; IOP = Intraocular pressure.

TABLE II - ADVERSE EVENTS (number of patients)

Events	Brimonidine	Placebo
Red eye	1	0
Dry mouth	3	0
Sedation	2	1
Headache	1	3
Blurred vision	0	1

(data not presented). The single patient who experienced subjective blurring of vision at the end of the placebo phase, when tested for best-corrected vision, retained his baseline visual acuity, but with a different optical correction.

Figure 1 shows the IOP mean value measured at baseline and at the end of each study phase. Mean IOP at the end of the washout was superimposable to the baseline (p=0.40). On brimonidine, mean IOP significantly decreased (p<0.001) from 17.1 ± 0.7 mmHg (baseline) to 15.1 ± 1.0 mmHg on day 1 (power = 90%, alpha = 7.5%), and to 13.9 ± 2.2 mmHg on day 30 (power = 90%, alpha = 1%). During the same phase, mean IOP on day 30 was significantly lower than mean IOP on day 1 (p=0.019, power = 80%, alpha = 10%). No appreciable IOP change was observed during the placebo phase. Figure 2 shows the chart obtained by plotting IOP values during brimonidine phase vs the baseline. As observable in this figure, 4 of 16 treated subjects (25%) had a ≥30% IOP decrease at the end of the brimonidine phase.

The diurnal profile of the IOP during each treatment phase (mean values ± standard deviation) is displayed in Figure 3. The brimonidine curve was significantly lower (p<0.01) than either baseline or placebo at different time points (i.e., at 10 am, 12 am, 2 pm, and 9 pm).

DISCUSSION

These data show that a cohort of normal tension eyes with glaucoma, exposed for 30 days to 0.2% brimonidine eyedrops twice daily, showed a significant decrease of IOP. During the placebo phase, however, IOP was superimposable to the prestudy baseline values. We can thus rule out any possible bias due to a regression-to-the-mean artefact. A twice-daily administration schedule might have introduced possible bias by enhancing the peak effect of the tested drug on round-the-clock IOP measuring. Actually, the readings at 10 am and 9 pm were two peak readings, the drug having been administered 1 to 2 hours before (see Patients and Methods for details). We addressed this issue by adopting the average of the two highest readings of the IOP profile for statistical analysis.

During the brimonidine phase, the IOP values seemed lower on day 30 than on day 1 (Fig. 1). The scatterplot in Figure 2 evidences a wide distribution of the mean IOP readings, showing that the response to the treatment phase was not strongly homogeneous. The results, however, are supported by a borderline significance, the alpha probability being as high as 10%, and need to be confirmed in adequately sized

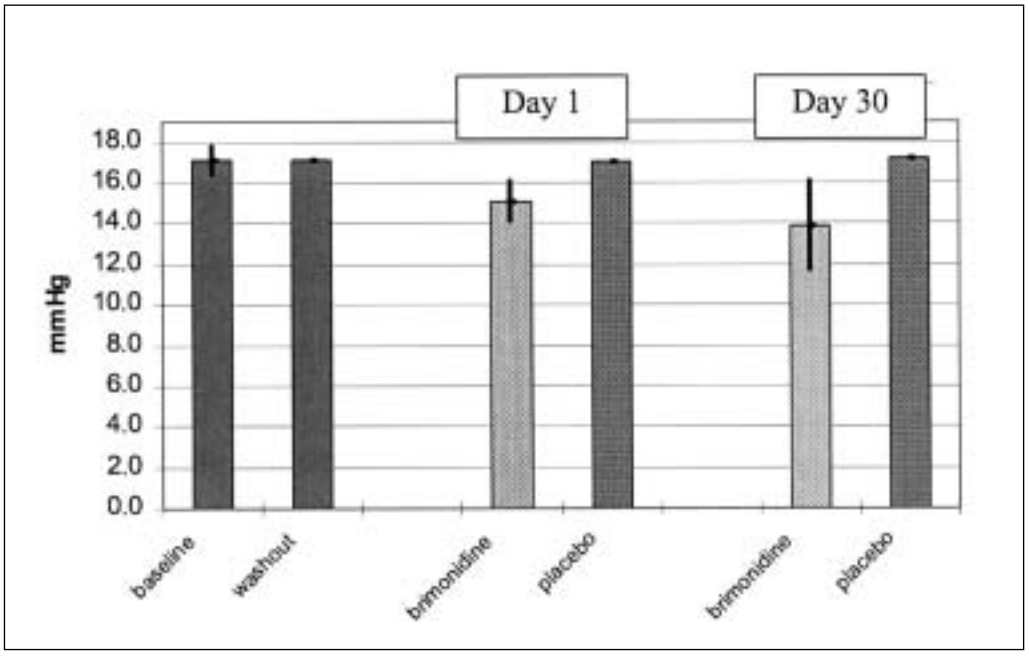

Fig. 1 - *Bars represent the mean intraocular pressure values (± standard deviation for baseline and brimonidine) measured at the scheduled time points for brimonidine and placebo (see Patients and Methods for details).*

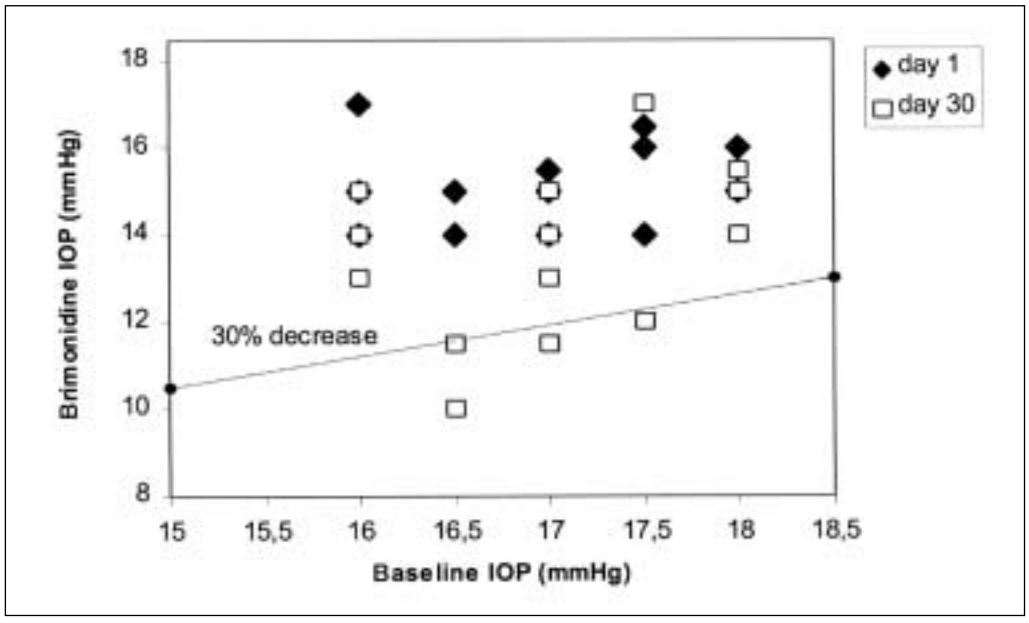

Fig. 2 - *Scatter shows intraocular pressure changes from the baseline (x axis) to day 1 and day 30 of the brimonidine treatment phase (y axis).*

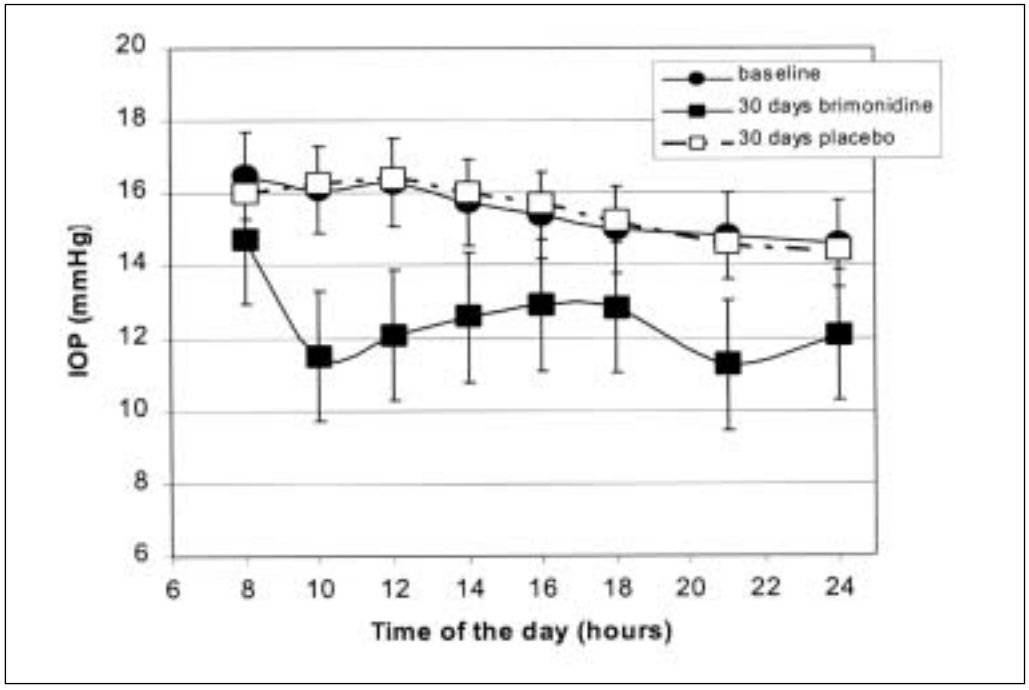

Fig. 3 - *Diurnal profile of the intraocular pressure (mean values ± standard deviation) during each treatment phase.*

prospective studies. Interestingly, Toris and coworkers, while measuring IOP and aqueous dynamics in ocular hypertensive patients during a 1-month treatment with 0.2% brimonidine twice daily, suggested that "...brimonidine-induced reduction in IOP... is associated initially with a decrease in aqueous flow, and after chronic treatment, with an increase in uveo scleral outflow" (6).

The 30-day follow-up is too short to establish a definite role for brimonidine in a disease that may take years to demonstrate progression. However, the length of our study is consistent with that adopted in

previous studies performed on normal tension glaucoma (7). Besides, brimonidine has been shown to remain effective as long as 3 years after initiating treatment in primary open angle glaucoma and ocular hypertension (5).

In conclusion, the data presented in our study show that 0.2% brimonidine twice daily can offer, in the short term, a significant IOP reduction in subjects with normal tension glaucoma.

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