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Influence of topical brimonidine on visual field in glaucoma

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PURPOSE. *We evaluated the efficacy of topical brimonidine in visual field preservation and/or improvement in eyes undergoing controlled glaucoma.*
METHODS. *Seventy eyes of patients were trained with two different visual field test strategies: The Octopus Tendency Oriented Perimetry (TOP) G1 and the Frequency Doubling Technology (FDT) 30°. Following 2-4 months of brimonidine treatment, there were significant improvements in visual field, as assessed using the TOP G1 strategy (p = 0.003). The FDT 30° test revealed no statistically significant differences.*
CONCLUSIONS. *These data support the results of other studies, which indicate that brimonidine may increase mean sensitivity in visual field tests. Since it is known that the control of intraocular pressure does not fully protect glaucomatous eyes from visual field loss, it is possible that the neuroprotective qualities of brimonidine may contribute to visual field preservation in glaucomatous eyes.* Eur J Ophthalmol 2001; 11 (Suppl 2): S67-S71

KEY WORDS. *Brimonidine, Glaucoma, IOP, Neuroprotection, Visual field*

INTRODUCTION

The aim of glaucoma therapy today is limited to achieving target control of intraocular pressure (IOP). However, even in the case of IOP control, visual field declines at a mean annual rate of 1.4% (1). This has led to interest in a new class of drugs with the ability to protect neurons from programmed cell death (apoptosis). Among the drugs currently used in glaucoma therapy, some have both IOP-lowering and neuroprotective properties, such as the α_2-agonist brimonidine (2,3). This group of drugs is therefore of particular interest.

Visual field tests are important tools for the diagnosis and follow-up of glaucomatous eyes. The purpose of the study is to evaluate the efficacy of treatment with topically applied brimonidine tartrate 0.2% bid on the visual field of glaucomatous eyes in the mid-term of 2-4 months.

METHODS

Study design

In order to reduce a learning effect (4-6), visual field tests were performed within a week prior to day 0. These results were rejected. On day 0, visual field tests and general evaluations, including IOP measurements, were carried out. These evaluations were repeated after 2-4 months. In addition, an intermediate evaluation of IOP was carried out to assess IOP control between days 30 and 50.

The Octopus Tendency Oriented Perimetry (TOP) G1 white–white strategy and the Frequency Doubling Technology (FDT) 30° threshold were selected for perimetry evaluations.

- The TOP G1 has been widely validated as a white–white strategy (7, 8).

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- The FDT 30° explores a smaller sub-population of retinal ganglion cells; namely a sub-class of the M ganglion cells connecting to the magnocellular layers of the lateral geniculate nucleus (9). It was developed for detection of early glaucomatous field defects (9), but is most useful in the detection of moderate and severe disease (10).

Patients

Seventy eyes of patients suffering from different types of glaucoma satisfied the inclusion criteria and were eligible for the study. Inclusion and exclusion criteria are summarized in Table I.

Statistical evaluation

Mean sensitivities (MS, [dB]) of TOP G1 and FDT 30° before and after treatment were used for statistical evaluation. The Kolmogrov-Smirnov test for normal distribution of these values was not significant, therefore, it was possible to assume normal distribution. Paired data of MS prior and post treatment for both TOP G1 and FDT 30° were analyzed with Student's t-test for paired data when patients satisfied visual field criteria.

RESULTS

Patients

Baseline and demographic characteristics of the group are described in Table II.

Visual field evaluations

After supplementary exclusions for visual field criteria, 51 cases were evaluated for differences in MS of TOP G1 before and after treatment. Statistically significant improvements were observed in 51 eyes examined with TOP G1 ($p = 0.003$) (Fig. 1). However, the FDT 30° did not detect statistically significant differences in 40 eyes examined, compared with baseline values ($p = 0.517$).

Although the sample was small for further statistical analysis, open angle glaucoma, in initial and moderate stages increased the likelihood of MS improvement after the treatment was assessed by TOP G1 strategy.

Fourteen (20%) cases were withdrawn either for allergy or ocular discomfort (n = 4) or for uncontrolled IOP needing supplementary treatment (n = 10).

TABLE I - INCLUSION AND EXCLUSION CRITERIA, VISUAL FIELD CRITERIA AND REASONS FOR STUDY WITHDRAWAL

Criteria	Characteristics
Inclusion criteria	• Glaucomatous patients • IOP controlled and visual field stability for at least the last 3 months, either with topical medication (other than brimonidine), laser or surgery
Exclusion criteria	• History of ocular surface disorders or topical drug allergy, diabetic retinopathy, macular degenerations • Contraindications for topical brimonidine • Suspect of potential poor compliance
Visual field criteria for exclusion	• Patients who score for more than 1/7 (False positive; FP + False Negative; FN) in TOP G1 • Patients who score for more than 2/19 (Fixation loss + FP + FN) in FDT 30°
Reasons for patient withdrawal	• Adverse event, including allergy or poor tolerability • Poor compliance • Failure to control IOP • Inability to satisfy the visual field criteria in the second visit. Both visual fields were withdrawn in these cases.

DISCUSSION

We observed an increase in MS in brimonidine-treated eyes in just 3 months when measured with TOP G1. In a study reported by Mirza et al (28) timolol 0.5% did not alter MS or mean deviation (MD) in the time-course of 90 days' treatment, although Vainio-Jylhä et al (29) found that timolol 0.25% and betaxolol 0.5% lead to an improvement in MS in the visual field measured with TOP after 1 year of treatment. While in the latter study (29) the MS decreased by approximately 0.5dB (no exact values given) in the first 3 months after the start of treatment with timolol or betaxolol, our results show an increase of nearly 1dB in mean MS after 3 months of treatment with brimonidine. In a 3-year trial comparing brimonidine 0.2% bid or timolol 0.5% bid with baseline visual field measures, Melamed et al (26) found that 95% of the patients in both treatment groups showed neither changes (within 5dB of baseline) nor an improvement (> 5dB of baseline) of the visual field measured with Humphrey Program 30-2 or TOP 32. No significant differences between the groups were found (26). Similarly, in a 1-year trial comparing brimonidine and timolol, 94% of patients in each group showed less than 5dB change in visual field, which was considered non-significant (13). LeBlanc et al (27) obtained results regarding the MD in a similar range using the Humphrey Program 30-2.

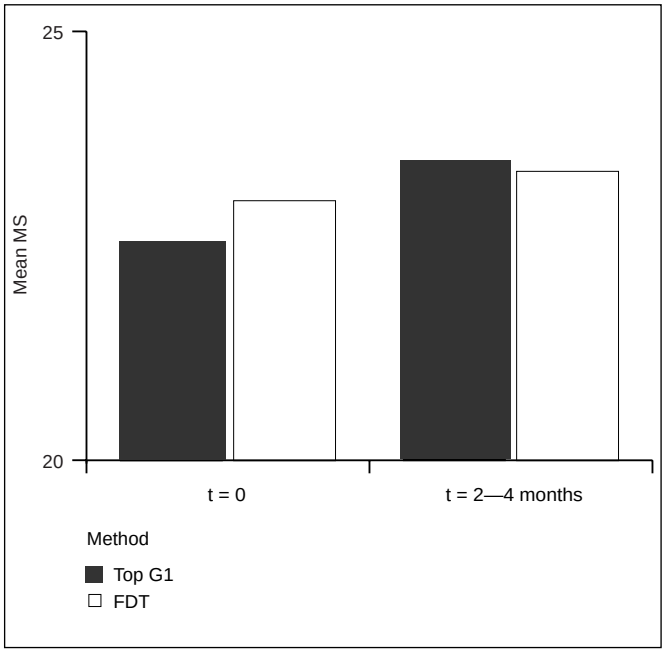

Fig. 1 - *Visual field changes before and after treatment with brimonidine.*

In our study reported here, FDT 30° failed to demonstrate any differences in MS. This might be due to earlier and less reversible damage on the small magnocellular sub-population, or on the smaller size of the sample, increased difficulty and time for exploration and the calculation of MS as the mean of only 19 areas (less definition).

TABLE II - BASELINE CHARACTERISTICS OF PATIENTS INCLUDED IN THE STUDY

Characteristics		**Trial disposition (n = 70)**
Gender	n; male:female	50:20
Age in years	mean ± SD (range)	53.4 ± 1.95 (23–83)
Eye	n; right:left	40:30
Evaluation of glaucoma, n (%)	initial	34 (48.5%)
	moderate	22 (31.4%)
	advanced	14 (20.0%)
Clinical diagnosis of glaucoma, n	Open angle glaucoma (OAG)	56
	Normal tension glaucoma (NTG)	6
	OAG + high myopia	13
	Miscellaneous	1

The results from our, and several previous, investigations indicate that brimonidine prevents visual field loss in glaucoma. Brimonidine is able to reduce IOP in ocular hypertensive patients, initially by decreasing aqueous humour secretion and after chronic treatment by increasing uveoscleral outflow (11,12). Previous studies have shown that the IOP-lowering effect of brimonidine is at least as effective as that of timolol (13) or betaxolol (2). However, since even with IOP control, visual field declines at a mean annual rate of 1.4% (1), the benefits of brimonidine in this area indicate that an additional mechanism is involved. Brimonidine has exhibited neuroprotective properties in different animal models (14,15), and topical instillation of brimonidine 0.2% leads to a concentration in the vitreous humour that is high enough to bind to and activate α_2-receptors in the human retina (16). It is possible that the neuroprotective qualities of brimonidine contribute to maintaining the visual field of glaucomatous eyes.

Several explanations of how brimonidine or other α_2-agonists exert their neuroprotective effects have been proposed, including:

- Activation of the PI3K pathway (17).
- Induction of phosphorylation of mitogen-activated protein kinase in the retina (18).
- Up-regulation of basic fibroblast growth factor (19).
- Hyperpolarization via interference with L-type calcium channels leading to decreased excitability of neurons (20), thus followed by decreased presynaptic liberation of glutamate (14).

Glutamate is elevated in the vitreous body of glaucomatous eyes (22), and the histological pattern of the loss of retinal ganglion cells observed in glaucoma and after experimental application of high glutamate levels is very similar. In a model of acute, high IOP in rats, brimonidine protected the retina from transient ischaemic stress and reduced the accumulation of glutamate and aspartate in the vitreous body (21). Brimonidine might also have an effect on ocular perfusion – the reduction of IOP possibly leading to an improvement, as shown by the reduction of corrected pattern standard deviation in blue–yellow perimetry (23). On the other hand, when measured with colour Doppler ultrasound, no alterations of haemodynamics in the posterior segment can be found after application of brimonidine (24). Also, in patients with ocular hypertension brimonidine 0.2% does not alter the retinal capillary blood flow (25).

CONCLUSIONS

Our results indicate that brimonidine might prevent visual field loss in a general population of glaucoma. White–white TOP G1 strategy showed an increase in mean sensitivity, while FDT 30º showed no significant differences over the time-course of 2-4 months. Further studies with non-paired data and parallel groups will be needed to demonstrate the efficacy of brimonidine in clinical neuroprotection over a longer period.

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