Graefe's Arch Clin Exp Ophthalmol
(2005) 243: 877–880

CLINICAL INVESTIGATION

DOI 10.1007/s00417-005-1160-7

Joseph R. Ferencz
Gila Gilady
Orly Harel
Michael Belkin
Ehud I. Assia

Topical brimonidine reduces collateral damage caused by laser photocoagulation for choroidal neovascularization

Received: 11 August 2004
Revised: 19 November 2004
Accepted: 31 January 2005
Published online: 23 March 2005

J. R. Ferencz (✉) · G. Gilady · O. Harel · E. I. Assia
Department of Ophthalmology,
Meir Medical Center,
44281 Kfar-Saba, Israel
e-mail: ferencz@zahav.net.il
Tel.: +972-9-7471527
Fax: +972-9-7472427

M. Belkin
Goldschleger Eye Research Institute,
Sheba Medical Center,
Tel Hashomer, Israel

M. Belkin
Sackler School of Medicine,
Tel-Aviv University,
Ramat Aviv, Israel

Abstract *Purpose:* To evaluate the neuroprotective efficacy of brimonidine applied topically to the eyes of patients undergoing laser treatment for extrafoveal or juxtafoveal choroidal neovascularization (CNV). *Method:* In this prospective, controlled, double-masked pilot study, 20 eyes were randomized to receive either brimonidine 0.2% (study group, 11 eyes) or placebo (matched control group, 9 eyes). Medications were topically applied twice a day during a period of 4–48 h before laser treatment and were continued for 1 month. *Results:* Two eyes in each group had severe visual loss owing to recurrence of CNV. In the remaining 16 eyes there was a significant improvement in the study group, but no improvement in the control group (P=0.027). *Conclusion:* Topical brimonidine improves the visual outcome of laser-treated classic extrafoveal or juxtafoveal CNV, possibly by protecting the neuroretina against collateral damage caused by the laser treatment.

Keywords Choroidal neovascularization · Laser photocoagulation · Neuroprotection

Introduction

Photodynamic therapy is considered the treatment of choice for several types of subfoveal choroidal neovascularization (CNV), but conventional focal laser treatment is still the standard procedure for extrafoveal or juxtafoveal CNV. Although the laser treatment is localized, it causes secondary degeneration leading to spread of the damage from the initially affected retinal cells to the surrounding healthy retinal tissue, including the fovea in certain cases. The phenomenon of secondary degeneration is common to all nervous system insults, engendering extension of the morphological and functional damage to tissues neighboring the original insult [8].

Lesions caused by laser photocoagulation have indeed been shown to extend beyond the area directly affected by the laser beam [1, 2]. Therapy intended to limit secondary degeneration is a subject of considerable laboratory and clinical research. A neuroprotective compound, memantine (Namenda; Forest Laboratories, USA), was recently approved for the treatment of Alzheimer disease and is undergoing clinical trials for glaucoma.

Brimonidine (Alphagan; Allergan, Irvine, CA, USA), an α_2-adrenergic receptor agonist used as an ocular hypotensive agent [12], shows neuroprotective activity in experimental animals after different types of insults [6, 7, 15, 16]. The neuroprotective effect appears to be mediated by up-regulation of survival factors such as fibroblast growth factor

[14] and the anti-apoptotic gene Bcl-2 [16]. The purpose of this study was to determine whether the extent of damage caused by the laser beam in the treatment of patients with CNV can be reduced by local application of a neuroprotective drug such as brimonidine.

Patients and methods

In this controlled, prospective, double-masked pilot study, brimonidine eyedrops were instilled in the eyes of patients undergoing laser treatment for extra- or juxtrafoveal CNV. Patients with age-related macular degeneration (AMD) and clinically suspected CNV were examined by fluorescein angiography. All consecutive patients with confirmed classic extra- or juxtafoveal CNV were included in the study and underwent focal laser photocoagulation according to the protocol of the Macular Photocoagulation Study Group (MPS) [9]. All patients gave their written informed consent before treatment. Approval for the study was obtained from the Ethics Committee of the Meir Medical Center. Prior to laser treatment the patients were randomized to receive either topical brimonidine 0.2% or a placebo (artificial tears). The medications were applied topically twice a day starting at the time of diagnosis (4–48 h prior to laser treatment) and were continued twice daily for 1 month afterwards. Before undergoing laser treatment, and again 1 and 2 months after lasering, all patients underwent tests of Snellen visual acuity, central 10-deg automated visual field (Humphrey,10-2 threshold test), gross color vision (Ishihara plates), and contrast sensitivity (Vistech 6500, Dayton, Ohio, USA). The data were analyzed using SPSS 12.0 software (SPSS, Chicago, IL). A probability level of 0.05 was set as the limit of statistical significance.

Table 2 Initial and final visual acuity in the brimonidine-treated and control groups

	Initial VA	Final VA	*p*
	Mean±SD	Mean±SD	
Whole group			
Brimonidine (*n*=11)	0.391±0.234	0.532±0.327	0.165
Placebo (*n*=9)	0.400±0.250	0.389±0.280	0.834
Excluding four patients with subfoveal recurrence			
Brimonidine (*n*=9)	0.400±0.269	0.633±0.265	0.027
Placebo (*n*=7)	0.429±0.275	0.443±0.299	0.818

Results

All eligible eyes between June 1999 and January 2000 were included in this study. Eyes were randomly enrolled to the treatment and control groups. Nineteen patients (20 eyes) were treated in this study. There were 13 men and 6 women, with a mean age of 76.9 years (range 65−92 years). After giving their written consent, the patients were treated on a random basis with either brimonidine 0.2% (11 eyes; study group) or placebo (nine eyes; control). Both eyes of one patient with bilateral CNV were included in this study. One eye was assigned randomly to the study group and the other one to the control group. Initial visual acuity ranged between 0.8 (6/7.5) and 0.1 (6/60) in both the study group and the control group. Table 1 presents the baseline data of the study group (group 1) compared with the placebo group (group 2). There were no significant differences between these two groups in any of the baseline parameters. Two patients in each group had recurrence of CNV into the subfoveal area after the photocoagulation, resulting in severe loss of vision. Analysis of the results (paired *t*-test) showed a trend for a better visual acuity outcome in the brimonidine-

Table 1 Baseline data

	Group 1 (*n*=11)		Group 2 (*n*=9)		*p*
	Mean±SD	Range	Mean±SD	Range	
Age	76.2±7.3	65–92	7.8±7.3	67–90	0.63
Visual acuity	0.39±0.24	0.1–0.8	0.4±0.28	0.1–0.8	0.84
Color vision[a]	11.6±5.5	0.2–0.9	10.3±5.5	2–14	0.63
Visual field					
MD	(−)6.93±1.54	(−)15.74−(−)1.15	(−)7.39±1.21	(−)13.93−(−)3.39	0.82
PSD	3.93±0.50	1.36–6.98	4.36±0.74	2.48–9.54	0.63
SF	2.52±0.33	1.3–4.3	2.45±0.23	1.3–3.8	0.89
CPSD	4.69±0.58	0.0–6.8	3.51±0.88	0–9.2	0.52
Contrast sensitivity					
1.5 c/d	7.43±3.93	0–30	9.17±5.19	0–30	0.79
3 c/d	11.71±4.47	0–30	16.67±9.80	0–60	0.64
6 c/d	10.57±8.36	0–60	10.00±1.71	0–30	0.96
12 c/d	4.29±2.77	0–20	2.50±1.33	0–10	0.61
18 c/d	1.14±0.74	0–4	1.33±1.84	0–8	0.90

SD standard deviation; MD mean deviation, PSD pattern standard deviation, SF short-term fluctuation, CPSD corrected pattern standard deviation; c/d spatial frequency (cycles per degree)
[a]Number of Ishihara charts recognized (out of 14)

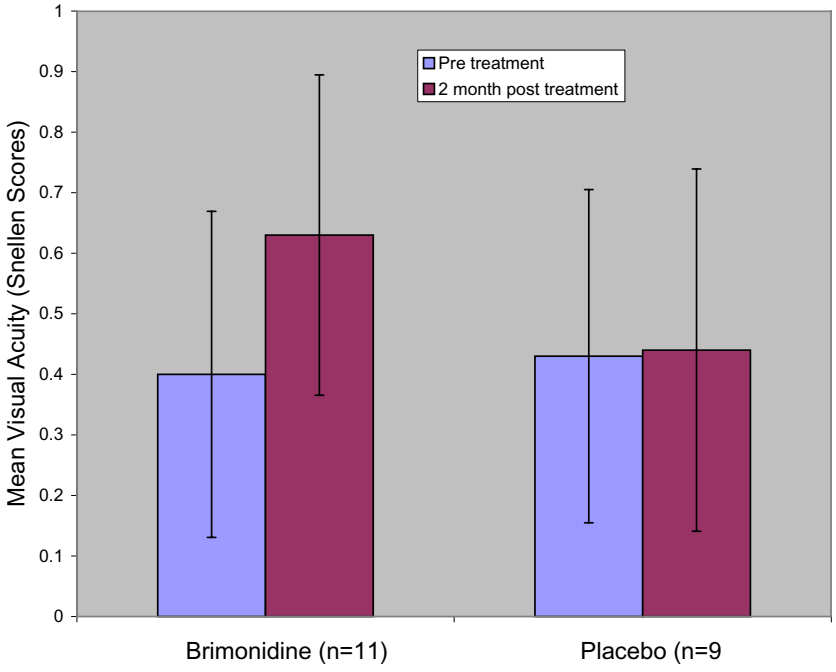

Fig. 1 Mean visual acuity and standard deviation in 16 eyes treated with brimonidine (2%) or placebo (artificial tears) with no recurrence of subfoveal CNV after laser photocoagulation. The significance of the difference in visual acuity between brimonidine-treated and placebo-treated eyes, calculated by paired *t*-test, is P=0.027

treated group, but the difference was not significant (Table 2). When the four patients with subfoveal recurrence were excluded from the analysis, the study group patients showed an improvement of 2.33 Snellen lines, in contrast to the controls, in whom no change was seen (p=0.027; Table 2, Fig. 1).

Tests of contrast sensitivity, visual field, and color vision revealed no significant differences between the study and the control groups.

Discussion

The irreversible loss of vision that occurs in some eye diseases is often an outcome of degeneration of retinal cells, which (being part of the central nervous system) cannot regenerate after injury. Studies have shown that primary damage to the retina caused by laser photocoagulation usually spreads to adjacent healthy cells [1, 2]. This "secondary degeneration", which results from the secretion of neurotoxins (glutamate, free radicals, and others) by the injured neurons, can lead to significant progression of the morphological and functional damage [8].

Studies have demonstrated the neuroprotective properties of agents that act, for example, as *N*-methyl-D-aspartate (NMDA) antagonists [4, 13]. Betaxolol, a β-blocker that decreases intraocular pressure (IOP), protects rabbit retinal cells from ischemic damage when applied as an intraperitoneal or intravitreal injection or topically (as eyedrops) [10, 11]. The α2-adrenoreceptor agonist brimonidine, another ocular hypotensive drug, decreases RGC loss when injected intraperitoneally immediately after a partial crush injury of the rat optic nerve [17]. The β-blocker timolol, which reduces IOP as effectively as brimonidine, did not have the same neuroprotective effect. In another study, early treatment with brimonidine decreased RGC loss in a model of ocular ischemia in rats. In that study brimonidine prevented an increase in the concentration of glutamate and aspartate in the vitreous body, possibly reflecting its neuroprotective activity [3]. Furthermore, it was shown to improve contrast sensitivity in eyes with POAG [5].

In the present study, we instilled brimonidine eyedrops or placebo in patients' eyes before and after laser photocoagulation for extra- and juxtafoveal CNV. Analysis of the visual outcome in the two treatment groups revealed a tendency towards better visual acuity in the study group than in the controls, but the difference was not significant, possibly because of the small sample size and the wide range of baseline visual acuity. Our primary objective in this study was to investigate the efficacy of brimonidine in reducing secondary degeneration in eyes that were successfully treated by laser photocoagulation, i.e., without recurrence of CNV, which can cause severe loss of vision and is a not uncommon complication of laser photocoagulation in patients with AMD. We therefore repeated our analysis of visual outcome, this time excluding the four eyes (two from each group) with subfoveal recurrence. This analysis showed that the visual outcome of the brimonidine-treated eyes was significantly better than in the eyes treated with placebo. This finding is probably due to the neuroprotective effect of brimonidine, which minimizes the visual loss due to secondary degeneration resulting from laser-induced damage to adjacent areas, including the fovea [8]. It is probable that brimonidine acted to lessen the extent of the secondary degeneration

induced by noxious substances emitted by cells directly destroyed by the laser radiation. As brimonidine has an anti-apoptotic effect [14, 16] secondary degeneration of cells around the primary lesion, which occurs by apoptosis, was limited and thus the morphological and functional damage sustained by the treated eyes was reduced.

The results of this small pilot study allow us to tentatively conclude that topical administration of brimonidine before and after focal laser photocoagulation for treatment of extra- or juxtafoveal CNV can improve the visual outcome and suggest that this finding can be attributed to the known neuroprotective effect of brimonidine. A randomized, double-masked study with a larger number of patients is needed to confirm these results.

References

1. Brancato R, Pece A, Avanza A, Radrizzani E (1990) Photocoagulation scar expansion after laser therapy for choroidal neovascularization in degenerative myopia. Retina 10:239–243
2. Dastgheib K, Bressler SB, Green WR (1993) Clinicopathologic correlation of laser lesion expansion after treatment of choroidal neovascularization. Retina 13:345–352
3. Donello JE, Padillo EU, Webster ML, Wheeler LA, Gil DW (2001) alpha(2)-Adrenoreceptor agonists inhibit vitreal glutamate and aspartate accumulation and preserve retinal function after transient ischemia. J Pharmacol Exp Ther 296:216a–223a
4. Ettaiche M, Fillacier K, Widmann C, Heurteaux C, Lazdunski M (1999) Riluzole improves functional recovery after ischemia in the rat retina. Invest Ophthalmol Vis Sci 40:729–736
5. Evans DW, Hosking SL, Gherghel D, Bartlett JD (2003) Contrast sensitivity improves after brimonidine therapy in primary open angle glaucoma: a case for neuroprotection. Br J Ophthalmol 87:1463–1465
6. Lafuente MP, Villegas-Perez MP, Sobrado-Calvo P, Garcia-Aviles A, Miralles de Imperial J, Vidal-Sanz M (2001) Neuroprotective effects of alpha(2)-selective adrenergic agonists against ischemia-induced retinal ganglion cell death. Invest Ophthalmol Vis Sci 42:2074–2084
7. Levkovitch-Verbin H, Harris-Cerruti C, Groner Y, Wheeler LA, Schwartz M, Yoles E (2000) RGC death in mice after optic nerve crush injury: oxidative stress and neuroprotection. Invest Ophthalmol Vis Sci 41:4169–4174
8. Lynch DR, Dawson TM (1994) Secondary mechanisms in neuronal trauma. Curr Opin Neurol 7:510–516
9. Macular Photocoagulation Study Group (1994) Laser photocoagulation for juxtafoveal choroidal neovascularization. Five-year results from randomized clinical trials. Arch Ophthalmol 112:500–509
10. Osborne NN, Cazevieille C, Carvalho AL, Larsen AK, DeSantis L (1997) In vivo and in vitro experiments show that betaxolol is a retinal neuroprotective agent. Brain Res 751:113–123
11. Osborne NN, DeSantis L, Bae JH, Ugarte M, Wood JP, Nash MS, Chidlow G (1999) Topically applied betaxolol attenuates NMDA-induced toxicity to ganglion cells and the effects of ischaemia to the retina. Exp Eye Res 69:331–342
12. Schuman JS, Horwitz B, Choplin NT, David R, Albracht D, Chen K (1997) A 1-year study of brimonidine twice daily in glaucoma and ocular hypertension. A controlled, randomized, multicenter clinical trial. Chronic Brimonidine Study Group. Arch Ophthalmol 115:847–852
13. Solberg Y, Rosner M, Turetz J, Belkin M (1997) MK-801 has neuroprotective and antiproliferative effects in retinal laser injuries. Invest Ophthalmol Vis Sci 38:1380–1389
14. Wen R, Cheng T, Li Y, Cao W, Steinberg RH (1996) Alpha 2-adrenergic agonists induce basic fibroblast growth factor expression in photoreceptors in vivo and ameliorate light damage. J Neurosci 116:5986–5992
15. Wheeler LA, Gil DW, WoldeMussie E (2001) Role of alpha-2 adrenergic receptors in neuroprotection and glaucoma. Surv Ophthalmol 245[Suppl 3]: S290–294; discussion S295–296
16. WoldeMussie E, Ruiz G, Wijono M, Wheeler LA (2001) Neuroprotection of retinal ganglion cells by brimonidine in rats with laser-induced chronic ocular hypertension. Invest Ophthalmol Vis Sci 42:2849–2855
17. Yoles E, Wheeler LA, Schwartz M (1999) Alpha2-adrenoreceptor agonists are neuroprotecrive in a rat model of optic nerve dgeneration. Invest Ophthalmol Vis Sci 40:65–73