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ARTICLE

Effect of brimonidine tartrate 0.15% on scotopic pupil size and upper eyelid position: controlled trial

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Abstract

Background To evaluate the effect of brimonidine tartrate 0.15% ophthalmic solution on pupil size under scotopic condition and upper eyelid position.

Methods This study comprised 72 eyes of 36 healthy subjects. A single drop of brimonidine tartrate 0.15% ophthalmic solution was instilled in the right eye and artificial tear was instilled in the left eye. Pupil size was measured using an infrared pupillometer under scotopic condition before and at 30 min, 2, 4, 6, 8 and 10 h after instillation. Measurement of margin reflex distance 1 (MRD1) was performed using a millimetre ruler before and after at 10 min after instillation.

Results The mean age of the subjects was 32.19 ± 11.43 years (range 10–52 years), 17 were female and 19 were male. Before brimonidine instillation, the mean pupil size was 6.09 ± 1.03 mm in the brimonidine eyes and 6.06 ± 1.04 mm in the control eyes. There was a significant decrease in mean pupil size at 30 min (4.45 ± 1.04), 2 h (4.49 ± 1.06), 4 h (4.59 ± 1.06), 6 h (4.89 ± 1.06) and 8 h (5.38 ± 1.02) after instillation compared to before in brimonidine eyes ($p < 0.001$ for all). There was a significant miosis continued for at least 6 h (5.95 ± 1.03) in control eyes ($p < 0.001$). There was no significant change in MRD1, before and after instillation both in brimonidine and control eyes.

Conclusions Brimonidine tartrate 0.15% had a significant miosis under scotopic condition for at least 8 h after instillation and had a significant miosis on the untreated eye for at least 6 h.

Introduction

Night-vision complaints such as glare, halo and star bursts are major concerns after laser refractive and premium intraocular lens surgery. In the postoperative period, patients with large pupils under scotopic conditions are high risk for night-vision complaints caused by corneal aberrations related to pupil size [1]. These complaints may be improved with miosis induced by pilocarpine. However, ciliary spasm discomfort continues to limit its use [2].

Brimonidine tartrate 0.15% is a highly selective α-2 adrenergic receptor agonist. It has been used as an anti-glaucoma drug [3]. Studies have shown that brimonidine, used twice daily for 12 months, was safe and effective in lowering intraocular pressure with minimal side effects in glaucomatous and ocular hypertensive patients [4, 5]. Brimonidine decreases pupil size in the dark and therefore may be useful in decreasing night-vision difficulties [6, 7]. Also, it has few α-1 adrenoreceptor-mediated ocular side effects, and has minimum deleterious effects on the cardiopulmonary system [5].

Botulinum toxin injection to the upper third of the face is a common cause of transient upper eyelid ptosis. Topical apraclonidine 0.5% eyedrop treatment is recommended in cases of transient ptosis [8]. The phenylephrine test is generally used to determine patients with blepharoptosis who can be candidates for Muller muscle-conjunctival resection [9]. Furthermore, phenylephrine may not be the

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optimal agent to fully reveal the potential contractility of Muller muscle. It has been reported that Muller resection could also be successful in patients in whom the phenylephrine test result is negative [10]. Studies showed that the predominant adrenergic receptors are of the α-1 and α-2 subtypes in Muller muscle and of the β1 subtype in the levator muscle [11, 12].

Apraclonidine 0.5% is an α-2 adrenergic receptor agonist. Its main indication is glaucoma, although eyelid retraction is well described as a side effect. Similarly, brimonidine 0.15% is expected to cause eyelid retraction by increasing Muller muscle tone. On the contrary, a recent study has shown that brimonidine 0.2% was not effective on upper eyelid position [13].

To the best of the authors' knowledge, there is no study evaluating the effect of brimonidine tartrate 0.15% on pupil size and upper eyelid position at the same time. The aim of our study was to evaluate the duration of the effect of brimonidine tartrate 0.15% on pupil size and its effect on the upper eyelid position.

Methods

This nonrandomised controlled clinical study comprised 72 eyes of 36 healthy subjects. The study was conducted in accordance with the Declaration of Helsinki, and informed consent was obtained from each subject. All subjects underwent a complete ophthalmic examination including refraction, best-corrected visual acuity (BCVA), slitlamp biomicroscopy, intraocular pressure measurement and fundus examination. Exclusion criteria included pregnancy, pupil irregularities, anisocoria of bigger than 1 mm, systemic or ocular medications, contact lens wear, ptosis, dermatochalasis, any systemic disease, previous ocular or eyelid surgery, retinal pathology, corneal opacity, cataract, glaucoma, pterygium, poor fixation and BCVA of <20/20.

A single drop of brimonidine tartrate 0.15% ophthalmic solution (Alphagan P®, Allergan Inc., Waco-Texas, USA) was instilled in the inferior fornix in the right eye and artificial tear (Artelac Advanced®, B&L Inc., USA) was instilled in the left eye. Pupil size was measured using an infra-red pupillometer (Colvard, Oasis Medical Inc., Glendora, CA, USA) under scotopic condition (1 cd/m^2) before and at 0.5, 2, 4, 6, 8 and 10 h after instillation. The subjects were dark-adapted for 3 min before each measure. Measurement of margin reflex distance 1 (MRD1) was performed before and after at 10 min after instillation. The measurements were made with a millimetre ruler with the subject looking straight ahead and the frontal plane of the face in a vertical position. All measurements were made in the same room lighting condition by the same examiner (İ.T). Statistical analysis was performed with analysis of variance test for repeated measurements. Data were analysed in SPSS 22.0 software (IBM Corp., Armonk, New York, USA). A P value < 0.05 was considered statistically significant.

Table 1 Pupil size in the brimonidine and control eyes in all intervals.

Time	Eyes	Mean ± SD (mm)	Min–Max (mm)
Baseline	Brimonidine	6.09 ± 1.03	4.7–7.9
	Control	6.06 ± 1.04	4.2–8.6
After 30 min	Brimonidine	4.45 ± 1.04[a]	3.3–6.7
	Control	5.86 ± 1.17[a]	4.3–9.0
After 2 h	Brimonidine	4.49 ± 1.06[a]	3.3–6.8
	Control	5.76 ± 1.12[a]	4.2–8.7
After 4 h	Brimonidine	4.59 ± 1.06[a]	3.4–6.9
	Control	5.67 ± 1.27[a]	4.1–8.5
After 6 h	Brimonidine	4.89 ± 1.06[a]	3.7–7.2
	Control	5.95 ± 1.03[a]	4.2–8.6
After 8 h	Brimonidine	5.38 ± 1.02[a]	4.2–7.6
	Control	6.05 ± 1.03	4.3–8.6
After 10 h	Brimonidine	6.05 ± 0.97	4.7–7.8
	Control	6.03 ± 1.13	4.3–9.0

[a]Statistically significant.

Results

The mean age of the subjects was 32.19 ± 11.43 years (range 10–52 years), 17 were female and 19 were male. Table 1 and Fig. 1 show the results. Before brimonidine instillation, the mean pupil size was 6.09 ± 1.03 mm in the brimonidine eyes and 6.06 ± 1.04 mm in the control eyes. There was no difference in pupil size before instillation between eyes ($p = 0.622$).

There was a significant decrease in mean pupil size at 30 min (4.45 ± 1.04), 2 h (4.49 ± 1.06), 4 h (4.59 ± 1.06), 6 h (4.89 ± 1.06) and 8 h (5.38 ± 1.02) after instillation compared with before in brimonidine eyes ($p < 0.001$ for all). Pupil size at 10 h (6.05 ± 0.97) did not change significantly in brimonidine eyes ($p = 0.054$).

There was a significant decrease in mean pupil size at 30 min (5.86 ± 1.17), 2 h (5.76 ± 1.12), 4 h (5.67 ± 1.27) and 6 h (5.95 ± 1.03) after instillation compared with before in control eyes ($p < 0.001$ for all). There was no significant change in pupil size at 8 h (6.05 ± 1.03) and 10 h (6.03 ± 1.13) in control eyes ($p = 0.379$ and $p = 0.314$, respectively).

Before brimonidine instillation, the mean MRD1 in both brimonidine eyes and control eyes was 4.15 ± 0.71 mm. At 10 min after instillation of brimonidine, there was no

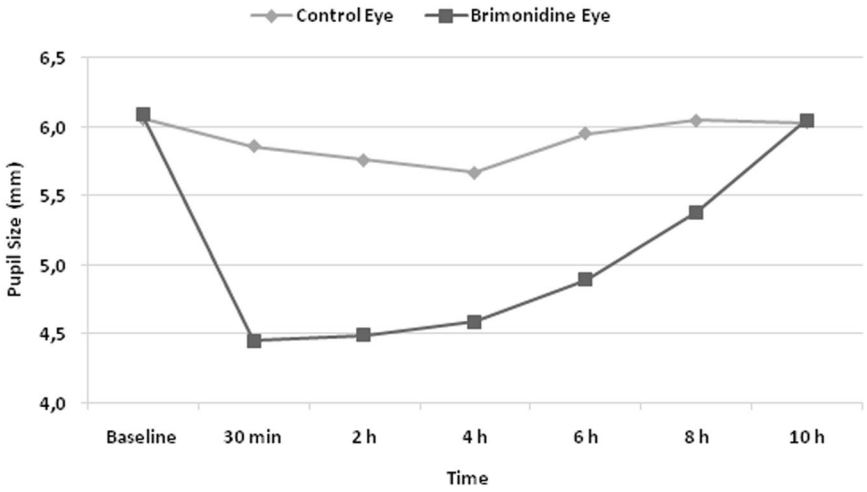

Fig. 1 Change of pupil size at different times in the brimonidine and control eyes under scotopic condition.

significant change in MRD1 neither in the brimonidine eyes (4.15 ± 0.71) nor in the control eyes (4.15 ± 0.71), ($p =$ 1.000 for both).

Discussion

Brimonidine tartrate 0.2% solution stimulates prejunctional α-2 agonist receptors, resulting in a reduction of norepinephrine release in the synapse. Norepinephrine contraction of the dilator muscles through an α-1 receptor is subsequently decreased, resulting in miosis [7]. In a study supported by Allergan, no significant changed occur in mean pupil size in treated eyes at any concentration of brimonidine tartrate (0.08%, 0.2% and 0.5%) [5]. However, brimonidine tartrate 0.2% instillation was found to have significant effect in reducing pupil size during visual field test [14]. Kesler et al. [15] reported brimonidine tartrate 0.2% causes significant miosis under scotopic conditions up to 6 h and in day light, the miotic effect was less pronounced. McDonald et al. [7] showed that brimonidine tartrate 0.2% had a significant effect in reduction pupil size under scotopic conditions up to 6 h but caused only mild miosis under photopic conditions. Shemesh et al. [16] found a significant reduction in pupil size under scotopic conditions up to 6 h after brimonidine tartrate 0.1% instillation. Thordsen et al. [17] reported that after brimonidine tartrate 0.15% instillation under scotopic conditions, pupil size was decreased by 1.0 mm or more in 100%, and 60% of eyes at 30 min and 6 h, respectively. Gerente et al. [3] reported that 1 drop of brimonidine tartrate 0.15% provided a long period of miotic effect, which was observed even after 8 h from its instillation. However, it also caused a reduction in pupil size of the untreated eye, which was greater 4 h from the instillation.

Similar to the previous study, we found that pupil size was significantly decreased under scotopic conditions up to 8 h after brimonidine tartrate 0.15% instillation. One of the most interesting results in the present study was a significant miosis continued for at least 6 h in untreated eyes. On the contrary, Gerente et al. [3] reported that miotic effect of brimonidine tartrate 0.15% in untreated eye only until 4 h from its instillation. We believe that, the miosis effect on the untreated eye may be related to systemic or nonsystemic absorption. In a way that supports our thinking a previous experimental rabbit study founded that brimonidine tartarate 0.2% was applied in one eye significant levels of the labelled drug were found in both optic nerves and tracts and olfactory bulb, with low drug levels in blood. The authors proposed that central nervous system (CNS) side effects of topical brimonidine may be due to absorption from a nonsystemic route to the CNS [18].

In the present study, there was no significant change in upper eyelid position, before and after instillation both in brimonidine and control eyes. This study is the first to evaluate the effect of brimonidine tartrate 0.15% on the upper eyelid position. Mendonça et al. [13] reported that after instillation of brimonidine 0.2%, there was no significant change in upper eyelid position. Although we used the 0.15% concentration of brimonidine, our results are consistent with these of Mendonça et al.

Many previous studies showed that, apraclonidine (1% or 0.5%), phenylephrine (2.5% or 10%) and naphazoline 0.05% elevated the upper eyelid. A study reported that brimonidine 0.2% and phenylephrine 0.12% had no effect on upper eyelid position [13, 19, 20]. These results show that elevation of the upper eyelid may be primarily related to drug concentration. Brimonidine at the of 0.15% concentration, which is effective in decreasing intraocular pressure, may not be enough for stimulation of the Muller muscle. Yazici and Beden [20] suggested that the α-2 receptors may not play as significant a role in elevating the upper eyelid as do α-1 receptors, and the elevating effect apraclonidine may be due to its weak α-1 activity.

In our study, we instilled one drop in the inferior fornix. As another possibility we think that, if two or more drops was instilled in the upper fornix while the patient's head was tilted backward, this may have a significant effect on the upper eyelid position.

There are some limitations to our study. First, the upper eyelid position measurements were made by simple technique used a millimetre ruler. Second, the sample size was relatively small. Another limitation in our study, the effect of brimonidine on pupil size in light and dark eyes was not evaluated.

In conclusion, this study demonstrated that brimonidine tartrate 0.15% has no effect in increasing the upper eyelid position. However, brimonidine tartrate 0.15% had a significant effect in reduction pupil size under scotopic conditions up to 8 h. Therefore, it may be effective for the reduction of night-vision disturbances after laser refractive and premium intraocular lens surgery.

Summary

What was known before

- Brimonidine tartrate 0.15% decreases pupil size in the dark and therefore useful in decreasing night vision difficulties.

What this study adds

- Brimonidine tartrate 0.15% decreases pupil size without changing the upper eyelid position, thereby reducing night-vision disturbances after laser refractive and premium intraocular lens surgery.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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