ARTICLE

Efficacy of brimonidine tartrate 0.2% ophthalmic solution in reducing halos after laser in situ keratomileusis

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PURPOSE: To quantitatively evaluate the effect of brimonidine tartrate 0.2% (Alphagan) on halo and pupil size in patients who had symptomatic night-vision difficulties after laser in situ keratomileusis (LASIK).

SETTING: Nune Eye Hospital, Seoul, Korea.

METHODS: This study comprised 28 eyes of 14 patients with symptomatic night-vision difficulties after LASIK. Pupil diameter was measured with a Colvard pupillometer (Oasis Medical, Inc.). Quantitative analysis of halos was performed by measuring the area using a new computerized method. Pupil size and halo size were evaluated under scotopic and normal room light conditions. Alphagan was administered, and the effect was measured after 30 minutes and 1, 6, 12, and 24 hours.

RESULTS: There was a statistically significant correlation between pupil size and halo size ($r = 0.527$; $P<.0001$; slope = 691.6 pixel/mm). Pupil size and halo size decreased significantly 30 minutes after Alphagan instillation under both luminance conditions (all $P<.0001$). Under normal room light, the pupil and halo remained decreased until the last measurement at 24 hours. Under scotopic conditions, the pupil returned to its preinstillation size at 24 hours while the halo remained decreased. The maximum effect on halos was observed after 6 hours, when the mean reduction over preinstillation size was 28.2% and 29.1% under normal room light conditions and scotopic conditions, respectively.

CONCLUSION: Alphagan effectively reduced halo size and pupil size in postoperative LASIK patients with night-vision symptoms.

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Night-vision difficulties such as glare and halos are major concerns after excimer laser refractive surgery. In the early postoperative period, patients with large pupils under scotopic conditions are at high risk for night-vision difficulties caused by corneal aberrations related to pupil size.[1]

Brimonidine tartrate 0.2% ophthalmic solution is a highly selective α-2 adrenergic receptor agonist that has been shown to reduce intraocular pressure (IOP) in patients with glaucoma[2] and to attenuate IOP elevation after anterior laser procedures with minimal side effects and good systemic tolerance.[3,4] It also decreases pupil size, especially under scotopic conditions. Although the reduction in pupil size under scotopic conditions may result in decreased night-vision difficulties, to our knowledge no study in the literature has demonstrated quantitative improvement in night-vision difficulties with brimonidine tartrate.

There are few methods to assess the degree of night glare disability, including the Brightness Acuity Tester, psychometric questionnaires, and the Night Vision Recording Chart; however, no gold-standard clinical tests are currently available.[5] Subjective observations of halos and disturbances caused by them after LASIK are often evaluated using a questionnaire. We introduce a new computerized method to quantify the severity of halos.

The purpose of our study was to evaluate the effect of brimonidine tartrate 0.2% (Alphagan) on pupil size and halos after laser in situ keratomileusis (LASIK) by quantitative analysis of halo size using a computerized method over a 24-hour period. We also evaluated the correlation between pupillometer-measured pupil size and computer-measured halo size.

PATIENTS AND METHODS

Of the 318 patients who had LASIK for myopia and astigmatism from January 2004 to March 2004 at Nune Eye Hospital, Seoul, Korea, 14 (28 eyes) were enrolled in this study. Inclusion criteria were uneventful LASIK for myopia with or

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without astigmatism performed at least 6 months before study enrolment, best corrected visual acuity (BCVA) better than 0.7 (Snellen chart), no previous intraocular surgery or other ophthalmic disorders that could influence glare disability or halo size, and history of stable night-vision disturbance for at least 3 months. Patients were asked about optical symptoms of night-vision disturbance (halo, star burst, and night-driving difficulties) in each eye separately. Also excluded were patients with ablations decentered by more than 1.0 mm, which was assessed by comparing the center of the optical zone between the preoperative and postoperative corneal topography.

All LASIK procedures were performed by the same surgeon (C.M.C.). The corneal flap was created with a Hansatome microkeratome (Bausch & Lomb Surgical) with a 160 µm head. The ablation was performed using the S4 excimer laser (Visx). Data on preoperative refractive error, ablation depth, and the optical and transition zones were collected.

A computer image-analysis program (Scion Corp.) was used to measure the size of the halo. The patients were seated 50 cm from a 17-inch, 75 Hz TFT-LCD monitor (1184 pixels × 864 pixels, Samsung) and asked to looked at a white circle (316 pixel unit) on the screen. The circle was a white light source with a luminance of 56.6 cd/m^2 that appeared in the center of the video monitor against a background luminance of 0.01 cd/m^2. Monocular testing was performed after the refractive error was corrected with manifest refraction and a +2.00 diopter addition to prevent accommodative pupil miosis. Eyeglasses were always used. The patients traced the boundary of the halo with a graphic tablet (Figure 1, *left*); the size of the halo was calculated in pixels (Figure 1, *right*). The halo measurement was repeated 3 times in each eye, and the mean size calculated in pixels. Pupil size was measured with a Colvard pupillometer (Oasis Medical, Inc.) after patients adapted to luminance conditions for 3 minutes. Pupil size and halo size were measured under 2 luminance conditions, scotopic (1 cd/m^2) and normal room light (5 cd/m^2). One drop of Alphagan was instilled in each eye. Halo size was measured after 30 minutes and 1, 6, 12, and 24 hours and pupil size, after 30 minutes and 1 and 24 hours.

Statistical analyses comparing the change in halo size and pupil size were performed using a repeated-measures analysis of variance (ANOVA). Post hoc multiple comparisons were performed when the difference was significant by repeated-measures ANOVA. Pearson correlations (r) and linear regression were used to examine the association between halo size and pupil size. The intraclass correlation coefficient was estimated to assess intraexaminer repeatability using 1-way random-effects analysis of variance (ANOVA). Intraexaminer repeatability was determined using the approach proposed by Bland and Altman,[6] which includes calculation of the repeatability coefficients and 95% limits of agreement between first-session and second-session measurements. A P value of 0.05 or less was considered statistically significant. All statistical calculations were performed using SPSS software (version 11.5, SPSS, Inc.).

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RESULTS

The mean age of the 14 patients was 26.3 years ± 5.2 (SD) (range 22 to 35 years). Table 1 shows the patients' characteristics. Of the 28 eyes, 28 had subjective symptoms of halo and 26 had star bursts; 3 patients reported night-driving difficulties. Table 2 shows the intraexaminer repeatability for halo-size measurements.

Pupil size and halo size decreased significantly after Alphagan instillation under normal room light and scotopic luminance conditions (all $P<.0001$, repeated-measures ANOVA). Table 3 shows the effect of Alphagan on pupil size and halo size under both luminance conditions. There was a significant correlation between pupil size and halo size ($r = 0.527$; $P<.0001$; slope = 691.6 pixel/mm) (Figure 2).

Normal Room Luminance

Pupils were statistically significantly smaller at the first measurement 30 minutes after Alphagan instillation. Pupil size decreased further 1 hour after instillation, although the change was not statistically significant. At the next measurement at 24 hours, the pupil was larger than in previous measurements but was statistically significantly smaller than before Alphagan was instilled (Figure 3). Halo size decreased significantly 30 minutes after instillation and remained stable through the measurement at 24 hours (Table 3 and Figure 4). The halos were smallest (mean 28.2% of original size) 6 hours after instillation. In 21 (87.5%) of 2 eyes, the halo was the smallest 6 or 12 hours after Alphagan instillation.

Scotopic Luminance

Under scotopic conditions, pupil size decreased 30 minutes and 1 hour after Alphagan instillation and returned to preinstillation size at 24 hours. Halo size continued to decrease until 1 hour after instillation and remained decreased through the measurement at 24 hours (Table 3). The maximum effect on halos was at 6 hours, at which time halos were a mean of 29.1% of the size before instillation. In 20 (87.0%) of 23 eyes, the halo was smallest 6 or 12 hours after Alphagan instillation (Figure 4).

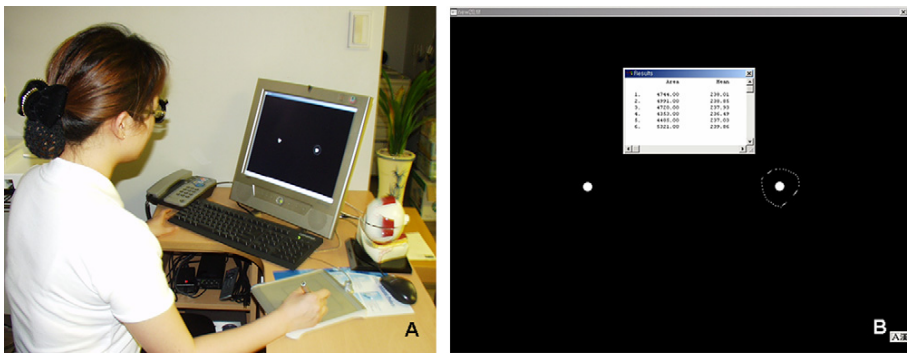

Figure 1. *Left*: A halo displayed on a TFT-LCD monitor with a graphic tablet. *Right*: Halo size was determined by measuring the area in pixels after the boundary of the halo was traced.

DISCUSSION

After refractive surgery, even patients with good BCVA can have night-vision disturbances. Factors known to increase the risks for such disturbances include large pupils, small optical treatment zones, and higher-order aberrations. Some studies[7–10] suggest that topical solutions such as brimonidine, dapiprazole, and aceclidine can be used to temporarily resolve night-vision disturbances by contracting the pupil. Although the effectiveness of these drugs in decreasing pupil size has been reported, no published study has directly evaluated their effect on night-vision disturbances. In this study, we found a quantitative improvement in halos, one of the most serious symptoms causing night-vision disturbance, after administration of Alphagan, whose active ingredient, brimonidine tartrate, causes miosis with few side effects.[9]

In our study, halo size under scotopic conditions remained decreased through 24 hours after Alphagan instillation; the maximum effect was at 1 hour and 12 hours. This indicates one drop a day helps not only patients who require short-term relief from halos but also those who may have the symptom for an entire night. Previous studies[8-10] did not evaluate how long miosis lasted because the last measurement was between 3 hours and 6 hours after administration.

Table 1. Patient characteristics.

Parameter	Value
Patients (n)	14
Eyes (n)	28
Mean age (y) ± SD	26.3 ± 5.2
Sex (n)	
Male	3
Female	11
Mean preop refractive error (D) ± SD	−6.49 ± 2.17
Mean ablation depth (μm) ± SD	83.03 ± 18.03
Mean optical zone (mm) ± SD	5.25 ± 0.34
Mean transition zone (mm) ± SD	7.12 ± 0.27

Although not statistically significant, the mean halo size was smallest at 6 hours and the mean pupil size was smallest at 1 hour under both luminance conditions (normal room light and scotopic). As we measured pupil size only 30 minutes, 1 hour, and 24 hours after Alphagan instillation, it is possible that the pupil was the smallest between 6 hours and 24 hours. Pupil size and halo size became statistically significantly stable 30 minutes after instillation under room light conditions and 1 hour after instillation under scotopic conditions. As the pupil is bigger under scotopic conditions, it is likely that more time is needed to reach Alphagan's maximum effect on pupil and halos.

Multiple comparisons with Bonferroni correction were performed to compare the measurements taken at different time points. The Bonferroni method is one of the most widely used corrections to minimize type I error (false positive when there is no real difference) when interpreting significant variation between the means in 3 or more groups. However, its disadvantage is that it is conservative because although the *F* test in the ANOVA is significantly significant, no pair of means can be significantly different.[11] In our study, mean pupil size under scotopic condition 24 hours after Alphagan installation was not statistically significantly different from that before installation by multiple comparison with Bonferroni correction ($P = .162$). However, when the means in the 2 groups were compared by paired *t* test, the difference was statistically significant ($P = .027$). Thus, it may be

Table 2. Intraexaminer repeatability for patient's tracings of halo size.

Measure	Result
ICC (95% CI)	0.92 (0.90 to 0.93)
Repeatability coefficient	678.6
95% LoA (pixels)	−646.4 to 683.6

CI = confidence interval; ICC = intraclass correlation coefficient; LoA = limits of agreement

Table 3. Variations in pupil size and halo size after Alphagan instillation.

Condition/Measurement	Time After Instillation						*P* Value*
	0 Min	30 Min	1 Hr	6 Hr	12 Hr	24 Hr	
Room light							
Mean pupil size (mm) ± SD	5.2 ± 0.6	4.6 ± 0.6†,‡	4.4 ± 0.5†	NA	NA	4.7 ± 0.7†,‡	<.0001
Mean halo size (pixels) ± SD	1855.3 ± 277.3	885.6 ± 118.3†,‡	676.5 ± 82.8†	541.4 ± 91.3†	582.6 ± 94.8†	1124.9 ± 195.6†	<.0001
Scotopic							
Mean pupil size (mm) ± SD	6.4 ± 0.7	5.6 ± 1.0†,‡	5.04 ± 0.8†,‡	NA	NA	6.1 ± 0.9‡	<.0001
Mean halo size (pixels) ± SD	2626.8 ± 373.0	1341.0 ± 244.8†,‡	963.1 ± 153.2†,‡	766.3 ± 151.1†	782.4 ± 133.2†	1976.2 ± 423.6†	<.0001

NA = not applicable
*Repeated-measures analysis of variance
†$P \leq .05$ compared with 0 min
‡$P \leq .05$ compared with previous time

somewhat controversial to say the effect of Alphagan will last for 24 hours after instillation under scotopic conditions.

Only one report[12] has evaluated the reduction in halos after LASIK. However, the reduction was achieved using over-minused lenses, not an ophthalmic solution, and used a subjective scale on which patients approximated the percentage change from baseline. Few quantitative assessments of halos have been reported.[13,14] Pieh et al.[13] measured the halo size in subjects with multifocal intraocular lenses and Lackner et al.,[14] in LASIK patients. Both studies were done at the same institute using the Glare & Halo computer program (Tomey AG). Except for the computer program used, the basic settings for halo measurements are similar between the 2 previous studies and our study. However, in the previous studies, based on the patient's instructions, an operator used a cursor to distinguish the outer margin of the halo; in our study, the patients themselves traced the area of the halo using a graphic tablet.

Our method of quantifying halo size did not involve equipment or software developed for halo measurements. However, ours is the first study to show that symptomatic halos can be decreased by pupil constriction and to describe the quantitative change in halo size after instillation of brimonidine tartrate 0.2%, in this case Alphagan.

In conclusion, a single-drop instillation of Alphagan effectively decreased halos by contracting the pupil. Its effect began at 30 minutes, with the maximum effect 1 hour after administration under scotopic conditions.

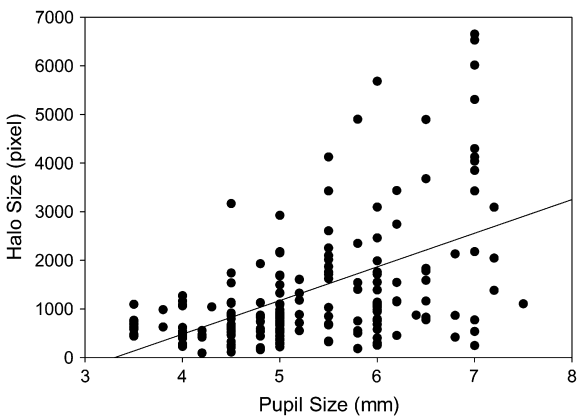

Figure 2. Regression and correlation between pupil (diameter, mm) and halo size (area, pixel).

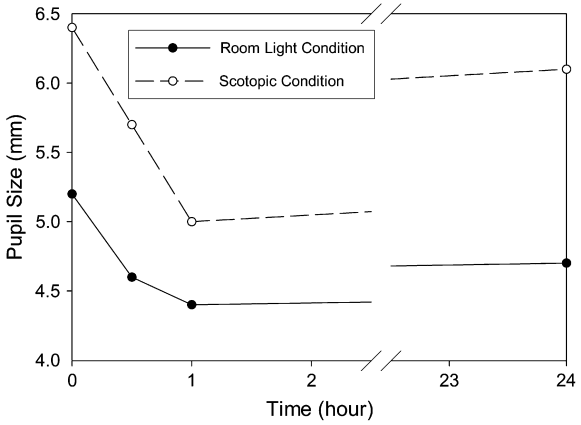

Figure 3. Pupil size at different times after installation of Alphagan.

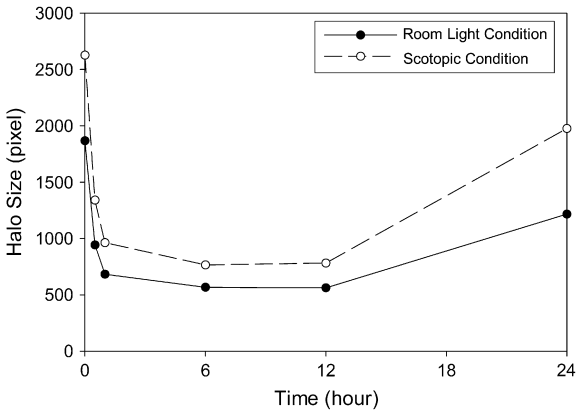

Figure 4. Halo size at different times after installation of Alphagan.

The halo size decreased from the preinstillation size by a mean of 71.8% and 70.9% under normal room light conditions and scotopic conditions, respectively. The action on halos lasted as long as 24 hours.

REFERENCES

1. Schallhorn SC, Kaupp SE, Tanzer DJ, Tidwell J, Laurent J, Bourque LB. Pupil size and quality of vision after LASIK. Ophthalmology 2003; 110:1606–1614
2. Katz LJ. Brimonidine tartrate 0.2% twice daily vs timolol 0.5% twice daily: 1-year results in glaucoma patients; the Brimonidine Study Group. Am J Ophthalmol 1999; 127:20–26
3. Barnebey HS, Robin AL, Zimmerman TJ, Morrison JC, Hersh SB, Lewis RA, Coleman AL, Cinotti DJ, Walt J, Chen KS, Kelley EP. The efficacy of brimonidine in decreasing elevations in intraocular pressure after laser trabeculoplasty. Ophthalmology 1993; 100:1083–1088
4. Chevrier RL, Assalian A, Duperré J, Lesk MR. Apraclonidine 0.5% versus brimonidine 0.2% for the control of intraocular pressure elevation after anterior segment laser procedures. Ophthalmic Surg Laser 1999; 30:199–204
5. Fan-Paul NI, Li J, Sullivan Miller J, Florakis GJ. Night vision disturbances after corneal refractive surgery. Surv Ophthalmol 2002; 47:533–546
6. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1:307–310
7. Randazzo A, Nizzola F, Rossetti L, Orzalesi N, Vinciguerra P. Pharmacological management of night vision disturbances after refractive surgery; results of a randomized clinical trial. J Cataract Refract Surg 2005; 31:1764–1772
8. Kesler A, Shemesh G, Rothkoff L, Lazar M. Effect of brimonidine tartrate 0.2% ophthalmic solution on pupil size. J Cataract Refract Surg 2004; 30:1707–1710
9. McDonald JE II, El-Moatassem Kotb AM, Decker BB. Effect of brimonidine tartrate ophthalmic solution 0.2% on pupil size in normal eyes under different luminance conditions. J Cataract Refract Surg 2001; 27:560–564
10. Marx-Gross S, Krummenauer F, Dick HB, Pfeiffer N. Brimonidine versus dapiprazole: influence on pupil size at various illumination levels. J Cataract Refract Surg 2005; 31:1372–1376
11. Altman DG. Practical Statistics for Medical Research. London, UK, Chapman and Hall, 1991; 211–212
12. Boxer Wachler BS, Hiatt D, Chou B, Christie JP. Reduction of pupil size and halos with minus lenses after laser in situ keratomileusis. J Refract Surg 2004; 20:149–154
13. Pieh S, Lackner B, Hanselmayer G, Zöhrer R, Sticker M, Weghaupt H, Fercher A, Skorpik C. Halo size under distance and near conditions in refractive multifocal intraocular lenses. Br J Ophthalmol 2001; 85:816–821
14. Lackner B, Pieh S, Schmidinger G, Hanselmayer G, Simader C, Reitner A, Skorpik C. Glare and halo phenomena after laser in situ keratomileusis. J Cataract Refract Surg 2003; 29:444–450