Contrast Sensitivity and Optical Quality of the Eye after Instillation of Timolol Maleate Gel-Forming Solution and Brinzolamide Ophthalmic Suspension

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Purpose: To investigate the influence of timolol maleate 0.5% gel-forming solution and brinzolamide 1% ophthalmic suspension on contrast sensitivity, ocular higher-order aberration (HOA), and corneal surface light scattering.

Design: Prospective, comparative study.

Participants: Forty normal volunteers were enrolled in this study.

Methods: We evaluated contrast sensitivity, ocular HOA, and corneal light scattering before and 2, 5, 10, and 15 minutes after instillation of antiglaucoma eyedrops. Contrast sensitivity function was assessed with the CSV-1000RN chart (Vector Vision Co., Greenville, OH). Higher-order aberration was measured for a 4-mm pupil using the Hartmann-Shack aberrometer (KR-9000PW; Topcon, Tokyo, Japan). Corneal surface light scattering was quantitatively evaluated by using the Scheimpflug camera (EAS-1000, Nidek, Aichi, Japan).

Main Outcome Measures: Time course of changes in contrast sensitivity, ocular HOAs, and corneal light scattering.

Results: Both timolol gel-forming solution and brinzolamide significantly decreased contrast sensitivity for at least 5 minutes after instillation ($P<0.01$). There were no significant differences in contrast sensitivity between the drugs at any time points. Higher-order aberration, such as third- and fourth-order aberrations and total HOAs, significantly increased after instillation of each drug ($P<0.001$). Timolol gel-forming solution significantly increased HOA up to 5 minutes after instillation ($P<0.05$), whereas brinzolamide significantly increased HOA for at least 2 minutes after instillation ($P<0.001$). Corneal surface scattering significantly increased for 5 minutes after instillation of brinzolamide ($P<0.01$), but not after instillation of timolol gel-forming solution.

Conclusions: Both drugs temporarily deteriorate contrast sensitivity function and optical quality of the eye. However, the mechanism underlying contrast sensitivity reduction seems to be different between the drugs. The reduction may be mainly attributed to increased HOA after instillation of timolol gel and increased light scattering after instillation of brinzolamide.

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Although a growing number of options have been available in the medical treatment of patients with glaucoma and ocular hypertension during the last decade,[1] topical beta-blockers remain the first- or second-line therapy in the management of glaucoma.[2–4] Above all, timolol maleate has been available as a solution to reduce intraocular pressure (IOP) for decades and is established as the accepted standard in treating patients with glaucoma and ocular hypertension.[5]

Approximately 10 years ago, a new preparation that combines timolol maleate and a heteropolysaccharide derived from gellan gum was released commercially. This preparation is liquid at room temperature but becomes a gel after reaction with cations in tears, and thus is called *timolol gel-forming solution.* This property prolongs retention of the drug on the ocular surface and promotes intraocular drug penetration, thereby permitting a convenient once-daily dosage. Although this once-daily dosing regimen is considered to improve patient compliance,[6] the gel form tends to cause transient blurring of vision after instillation. Previous studies showed that the incidence of blurred vision after instillation widely varies from 2.5% to 66.7%.[5,7–10] Such wide range can be attributed to the subjective assessment method of patient self-perception used in these studies. Shibuya et al[10] examined the incidence and duration of blurred vision in patients receiving timolol gel-forming solution by using a questionnaire and reported an incidence of 66.7% and a mean duration of 4.5 ± 7.3 minutes. Despite the widespread acceptance that timolol gel-forming solution contributes to the development of blurred vision after instillation as described, little is known about its effect on optical quality of the eye and quality of vision (QOV).

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Topical carbonic anhydrase inhibitors (CAIs) are generally used as an adjunctive (second- or third-line) therapy to other agents in practice. However, a relatively high incidence of ocular discomfort on instillation, such as ocular burning, stinging, and irritation, has been reported.[11–18] Pfeiffer et al reported that dorzolamide induced ocular burning and irritation in approximately 33% of patients,[19] which may be caused by the compound itself or the pH of 5.6.[14,15,19,20] Several years after the introduction of dorzolamide, brinzolamide was commercially released as the second topical CAI. This agent is formulated as an aqueous suspension at a pH of 7.5, which is closer to the physiologic pH than dorzolamide. Numerous studies have shown that brinzolamide produces less ocular discomfort on instillation than dorzolamide.[11–18] In addition, the IOP-lowering efficacy of brinzolamide 1% administered twice daily is equivalent to that of dorzolamide 2% given 3 times daily.[13,15,21] The less-frequent dosing regimen with brinzolamide may further improve patient compliance. However, the incidence of blurred vision for brinzolamide has been reported to be higher than that of dorzolamide.[13–16] The reported incidence ranges from 3.0% to 25%.[13–16] However, no studies have investigated the influence of brinzolamide on optical quality of the eye and QOV.

Because timolol gel-forming solution and brinzolamide ophthalmic suspension are widely used in practice[2–4,22] and many users have vision loss, it is crucial to examine the exact influence of these drugs on optical quality of the eye and QOV so that patients and practitioners are well informed of such information. Therefore, we objectively and quantitatively investigated the influence of timolol maleate gel-forming solution and brinzolamide ophthalmic suspension on the optical quality of the eye and QOV by evaluating ocular wavefront aberration, corneal surface scattering, and contrast sensitivity after instillation.

Subjects and Methods

Healthy volunteers at least 20 years of age without systemic and ocular diseases were recruited for this study. Subjects with regular use of any eyedrops or contact lenses and subjects with any problems in the fluidic kinetics of the tear (e.g., dry eye or epiphora) were excluded from the study. Two studies were conducted. In study 1, the influences of 2 antiglaucoma eyedrops on contrast sensitivity function were examined: timolol maleate 0.5% gel-forming solution (Timoptol XE, Banyu Pharmaceutical Co., Ltd., Tokyo, Japan) and brinzolamide 1% ophthalmic suspension (Azopt, Alcon Laboratories Inc, Fort Worth, TX). In study 2, the influences of these drugs on the optical quality of the eye were evaluated. The studies adhered to the tenets of the Declaration of Helsinki, and protocols were approved by the institutional review board of Tsukuba University Hospital. Written informed consent was obtained from each participant. A total of 40 subjects (23 in study 1 and 17 in study 2) were enrolled in these studies. All subjects had best-corrected visual acuity of 20/20 or better, had no symptoms of dry eye or epiphora, and showed normal tear film breakup time and Schirmer test value, which were tested at the time of enrollment. In addition, no abnormal findings were found on corneal topography in all subjects.

In study 1, the time course of changes in contrast sensitivity after instillation of each drug was evaluated. In 23 subjects (13 male and 10 female; 34.5±14.5 years, mean ± standard deviation), contrast sensitivity function was assessed with the CSV-1000RN chart (Vector Vision Co., Greenville, OH). The utility of this chart has been reported.[23,24] The chart uses figure optotypes, all of which were the same size and of low spatial frequency (2.4 cycles/degree). There are 8 contrast levels at 10.0%, 7.09%, 5.03%, 3.57%, 2.53%, 1.79%, 1.27%, and 0.90%. Each contrast level corresponds to a log contrast sensitivity of 1.00, 1.15, 1.30, 1.45, 1.60, 1.75, 1.90, and 2.05, respectively, that is, they are allocated at regular intervals of 0.15 log contrast sensitivity units. Each contrast level has 3 different figures, so that the total number of figures in the chart is 24. The test luminance level was automatically calibrated to 85 cd/m^2. Measurements started from the highest contrast level and advanced to the lower contrast levels in sequence. If subjects identified more than 2 figures at the same level, the contrast level was considered to be passed. The last contrast level passed was defined as the contrast level of the eye, and this value was converted to log contrast sensitivity for statistical analysis. The test was performed at a distance of 2.5 m with best-spectacle correction.

In study 2, the time course of changes in ocular higher-order aberration (HOA) and light scattering in 17 subjects (6 male and 11 female; 39.6±15.0 years) was investigated. Higher-order aberration was measured for a 4-mm pupil using the Hartmann-Shack aberrometer (KR-9000PW; Topcon, Tokyo, Japan).[25,26] The obtained data were expanded into a set of orthogonal Zernike polynomials, and HOA was calculated. The root mean square (RMS) of third-order Zernike components (Z_3^{-3} to Z_3^{3}) was used to represent coma-like aberrations, and the RMS of fourth-order Zernike components (Z_4^{-4} to Z_4^{4}) was used to represent spherical-like aberrations. Total HOAs were calculated as the RMS of the third- and fourth-order Zernike coefficients. Measurements were repeated at least 4 times for each eye, and the 3 best-focused images were selected and averaged. The averaged values were used for subsequent analyses.

Corneal surface light scattering was quantitatively evaluated using a charge-coupled device-equipped Scheimpflug camera (EAS-1000, Nidek, Aichi, Japan). This device was developed for the analysis of the anterior eye segment[27] and can measure scattered light intensity of the human lens,[28–30] intraocular lens,[31,32] posterior lens capsule,[33–37] and cornea.[38,39] The principles, technique, and reproducibility of the device have been described.[40,41] A cross-section of the anterior segment at 0-degree meridian was captured by the charge-coupled device camera for each subject and digitized for analysis. In the acquired Scheimpflug slit image, 3 points were selected along the anterior corneal surface. One point was plotted on the center of the cornea, and the other 2 points were plotted on both sides 1 mm apart from the center point. Densitometry was performed at these 3 points using image analysis software and recorded on a 256-step scale expressed as computer-compatible tape units.[34] The larger the value, the more bleached the point appears. The average value of the 3 points was calculated and used as the intensity of backward light scattering on the corneal surface.

In both studies, 1 eye (the right eye) of each patient was included in these studies. Subjects randomly received 1 drop of either drug, and the described examinations were performed before and 2, 5, 10, and 15 minutes after instillation. At intervals of more than 3 hours, another drug was applied to the same eye, and the measurements were repeated. In addition, timolol maleate 0.5% ophthalmic solution (Timoptol, Banyu Pharmaceutical Co., Ltd., Tokyo, Japan), which is a standard aqueous (non–gel-forming) formulation, was also used in the same manner to serve as a control drug. The obtained data were analyzed using repeated-measures analysis of variance (ANOVA) to assess the time course of changes in each parameter over 15 minutes. If significant differ-

ences were observed, the Dunnett post hoc test for multiple comparisons was performed to find time points showing significant difference from the baseline value. In addition, each parameter was compared between the drugs at each postoperative time point using 1-way ANOVA. Bonferroni's multiple comparison was performed if 1-way ANOVA was significant. All statistical analyses were performed using SPSS version 15.0J software (SPSS Inc., Chicago, IL); $P<0.05$ (or $P<0.016$ for Bonferroni's multiple comparison) was judged as statistically significant.

Results

The time course of changes in contrast sensitivity over 15 minutes is shown in Figure 1. Both timolol gel-forming solution and brinzolamide induced significant changes in log contrast sensitivity after instillation ($P<0.001$, repeated-measures ANOVA), although standard timolol solution did not change log contrast sensitivity ($P = 0.448$). Multiple comparison analysis revealed that log contrast sensitivity at 2 and 5 minutes after instillation was significantly lower than the pre-instillation values ($P<0.001$ and $P<0.001$ for timolol gel-forming solution, respectively, and $P<0.001$ and $P = 0.002$ for brinzolamide, respectively, Dunnett test). No significant decrease was found 10 minutes after instillation ($P = 0.077$ for timolol gel-forming solution and $P = 0.240$ for brinzolamide). The log contrast sensitivity completely returned to the baseline levels at 15 minutes after instillation ($P = 0.999$ and $P = 0.903$, respectively). On comparison of the 3 drugs, significant differences in log contrast sensitivity were found at 2 and 5 minutes after instillation ($P<0.001$ and $P = 0.015$, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.145$ and $P = 0.802$, respectively). Multiple comparison analysis showed significant differences between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.005$ for 5 minutes, Bonferroni's multiple comparison) and between brinzolamide and standard timolol solution ($P<0.001$ for 2 minutes). There were no significant differences in log contrast sensitivity between timolol gel-forming solution and brinzolamide at any time points ($P = 0.378–0.950$).

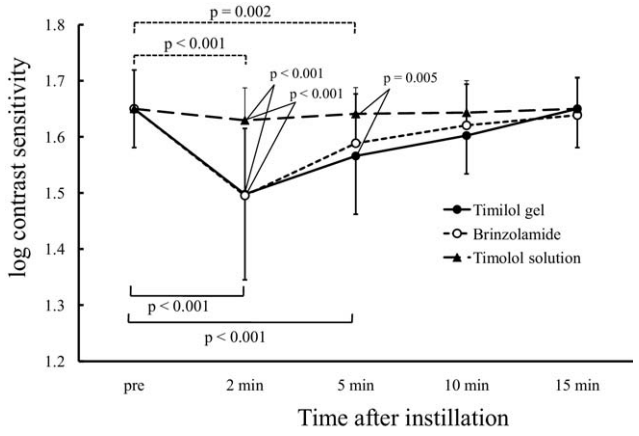

Figure 1. Time course of changes in contrast sensitivity over 15 minutes. Both timolol gel-forming solution and brinzolamide induced significant changes in log contrast sensitivity after instillation ($P<0.001$, repeated-measures ANOVA), although standard timolol solution did not change log contrast sensitivity ($P = 0.448$). Multiple comparison analysis revealed that log contrast sensitivity at 2 and 5 minutes after instillation was significantly lower than the pre-instillation values ($P<0.001$ and $P<0.001$ for timolol gel-forming solution; $P<0.001$ and $P = 0.002$ for brinzolamide, respectively, Dunnett test). No significant decrease was found at 10 minutes after instillation ($P = 0.077$ for timolol gel-forming solution; $P = 0.240$ for brinzolamide). The log contrast sensitivity completely returned to the baseline level at 15 minutes after instillation ($P = 0.999$ and $P = 0.903$, respectively). On comparison of the 3 drugs, significant differences in log contrast sensitivity were found at 2 and 5 minutes after instillation ($P<0.001$ and $P = 0.015$, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.145$ and $P = 0.802$, respectively). Multiple comparison analysis showed significant differences between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.005$ for 5 minutes, Bonferroni's multiple comparison) and between brinzolamide and standard timolol solution ($P<0.001$ for 2 minutes). There were no significant differences in log contrast sensitivity between timolol gel-forming solution and brinzolamide at any time points ($P = 0.378–0.950$). Graphs are expressed as the mean ± standard deviation. ANOVA = analysis of variance.

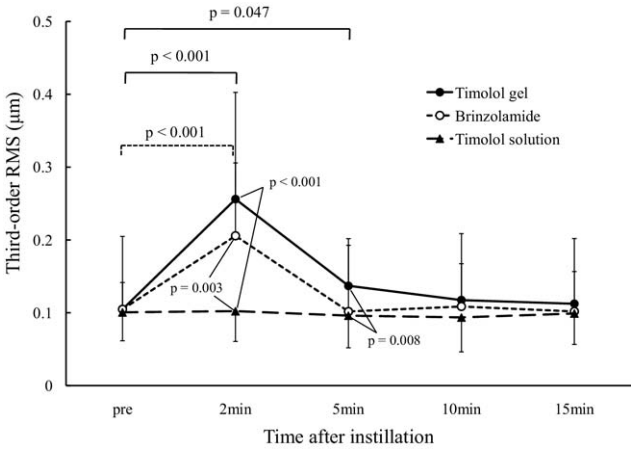

Figure 2. Time course of changes in third-order RMS. Third-order RMS significantly changed after instillation ($P<0.001$, repeated-measures ANOVA), increasing immediately after instillation and then decreasing toward the pre-instillation level. Compared with the pre-instillation values, significant increases were found at 2 and 5 minutes after instillation of timolol gel-forming solution ($P<0.001$ and $P = 0.047$, respectively, Dunnett test), but only at 2 minutes after instillation of brinzolamide ($P<0.001$). At 10 and 15 minutes after instillation, there were no significant increases in third-order RMS in both drugs ($P = 0.934–0.999$). On comparison of the 3 drugs, significant differences were found at 2 and 5 minutes after instillation ($P<0.001$ and $P = 0.016$, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.325$ and $P = 0.624$, respectively). Multiple comparison analysis showed significant differences between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.008$ for 5 minutes, Bonferroni's multiple comparison) and between brinzolamide and standard timolol solution ($P = 0.003$ for 2 minutes). Graphs are expressed as the mean ± standard deviation. RMS = root mean square.

The time courses of changes in HOA are shown in Figures 2 to 4. Both timolol gel-forming solution and brinzolamide significantly changed HOA, such as third-, fourth-, and total higher-order RMS after instillation ($P<0.001$, repeated-measures ANOVA), that is, all HOA components increased immediately after instillation and then returned toward the pre-instillation level. In contrast, standard timolol solution did not change HOA ($P = 0.388$, 0.485, and 0.208 for third-, fourth-, and total higher-order RMS, respectively). Compared with the pre-instillation values, third-order RMS showed significant increases at 2 and 5 minutes after instillation of timolol gel-forming solution ($P<0.001$ and $P = 0.047$, respectively, Dunnett test), but only at 2 minutes after instillation of brinzolamide ($P<0.001$). At 10 and 15 minutes after instillation,

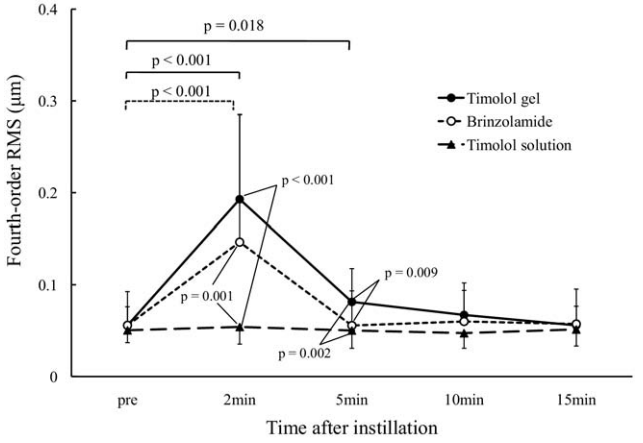

Figure 3. Time course of changes in fourth-order RMS. Fourth-order RMS showed significant increases compared with the pre-instillation values at 2 and 5 minutes after instillation of timolol gel-forming solution ($P<0.001$ and $P = 0.018$, respectively, Dunnett test), but only at 2 minutes after instillation of brinzolamide ($P<0.001$). There were no significant increases at 10 and 15 minutes after instillation ($P = 0.880$ and $P = 0.999$ for timolol gel-forming solution, and $P = 0.999$ and $P = 0.999$ for brinzolamide, respectively). On comparison of the 3 drugs, significant differences were found at 2 and 5 minutes after instillation ($P<0.001$ and $P = 0.004$, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.064$ and $P = 0.693$, respectively). Multiple comparison analysis showed significant differences between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.002$ for 5 minutes, Bonferroni's multiple comparison), between brinzolamide and standard timolol solution ($P = 0.001$ for 2 minutes), and between timolol gel-forming solution and brinzolamide ($P = 0.009$ for 5 minutes). Graphs are expressed as the mean ± standard deviation. RMS = root mean square.

there were no significant increases in third-order RMS for both drugs ($P = 0.934–0.999$). On comparison of the 3 drugs, significant differences in third-order RMS were found at 2 and 5 minutes after instillation ($P<0.001$ and $P = 0.016$, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.325$ and $P = 0.624$, respectively). Multiple comparison analysis showed significant differences between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.008$ for 5 minutes, Bonferroni's multiple comparison) and between brinzolamide and standard timolol solution ($P = 0.003$ for 2 minutes) (Fig 2). Similarly, fourth- and total higher-order RMS showed significant increases compared with the pre-instillation values at 2 and 5 minutes after instillation of timolol gel-forming solution ($P<0.001$ and $P = 0.018$ for fourth-order RMS, respectively, and $P<0.001$ and $P = 0.024$ for total higher-order RMS, respectively, Dunnett test), but only at 2 minutes after instillation of brinzolamide ($P<0.001$ for both RMS). There were no significant increases in RMS at 10 and 15 minutes after instillation ($P = 0.880$ and $P = 0.999$ for timolol gel-forming solution, respectively, and $P = 0.999$ and $P = 0.999$ for brinzolamide, respectively). When compared among the 3 drugs, significant differences in RMS were found at 2 and 5 minutes after instillation ($P<0.001$ and $P = 0.004$ for fourth-order RMS, respectively, and $P<0.001$ and $P<0.001$ for total higher-order RMS, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.064$ and $P = 0.693$ for fourth-order RMS, respectively, and $P = 0.068$ and $P = 0.124$ for total higher-order RMS, respectively). Multiple comparison analysis showed significant differences in fourth-order RMS between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.002$ for 5 minutes, Bonferroni's multiple comparison), between brinzolamide and standard timolol solution ($P = 0.001$ for 2 minutes), and between timolol gel-forming solution and brinzolamide ($P = 0.009$ for 5 minutes) (Fig 3). Significant differences in total higher-order RMS were also found between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.002$ for 5 minutes), between brinzolamide and standard timolol solution ($P<0.001$ for 2 minutes), and between timolol gel-forming solution and brinzolamide ($P = 0.010$ for 5 minutes) (Fig 4).

The time course of changes in corneal surface scattering is shown in Figure 5. There were no significant changes after instillation of timolol gel-forming solution ($P = 0.320$, repeated-measures ANOVA) or standard timolol solution ($P = 0.073$), whereas a significant change was noted after instillation of brinzolamide ($P<0.001$). Multiple comparison analysis revealed that corneal surface scattering increased at 2 and 5 minutes after instillation of brinzolamide compared with the baseline values ($P<0.001$ and $P = 0.002$, respectively, Dunnett test). When corneal surface scattering was compared among the 3 drugs, there were significant differences at 2 and 5 minutes after instillation (both $P<0.001$, 1-way ANOVA). Bonferroni's multiple comparison test showed significant differences between brinzolamide and standard timolol solution (both $P<0.001$ for 2 and 5 minutes) and between brinzolamide and timolol gel-forming solution ($P<0.001$ for 2 minutes and $P = 0.007$ for 5 minutes). However, no significant differences in corneal surface scattering were observed between timolol

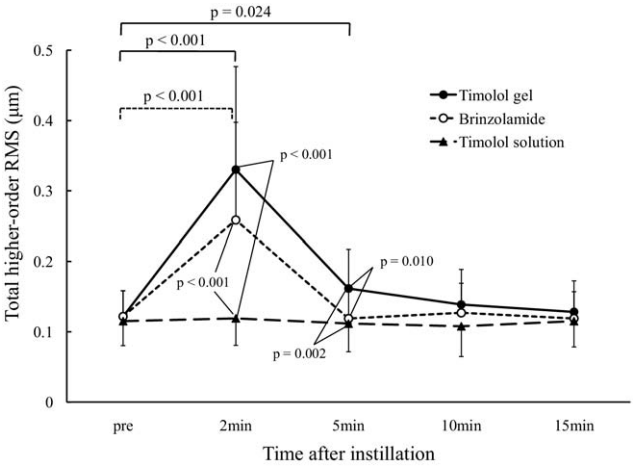

Figure 4. Time course of changes in total higher-order RMS. Total higher-order RMS showed significant increases compared with the pre-instillation values at 2 and 5 minutes after instillation of timolol gel-forming solution ($P<0.001$ and $P = 0.024$, respectively, Dunnett test), but only at 2 minutes after instillation of brinzolamide ($P<0.001$). There were no significant increases in total higher-order RMS at 10 and 15 minutes after instillation ($P = 0.896$ and $P = 0.999$ for timolol gel-forming solution, and $P = 0.999$ and $P = 0.996$ for brinzolamide, respectively). On comparison of the 3 drugs, significant differences were found at 2 and 5 minutes after instillation ($P<0.001$ and $P<0.001$, respectively, 1-way ANOVA), but not at 10 and 15 minutes after instillation ($P = 0.068$ and $P = 0.124$, respectively). Multiple comparison analysis showed significant differences between timolol gel-forming solution and standard timolol solution ($P<0.001$ for 2 minutes and $P = 0.002$ for 5 minutes, Bonferroni's multiple comparison), between brinzolamide and standard timolol solution ($P<0.001$ for 2 minutes), and between timolol gel-forming solution and brinzolamide ($P = 0.010$ for 5 minutes). Graphs are expressed as the mean ± standard deviation. RMS=root mean square.

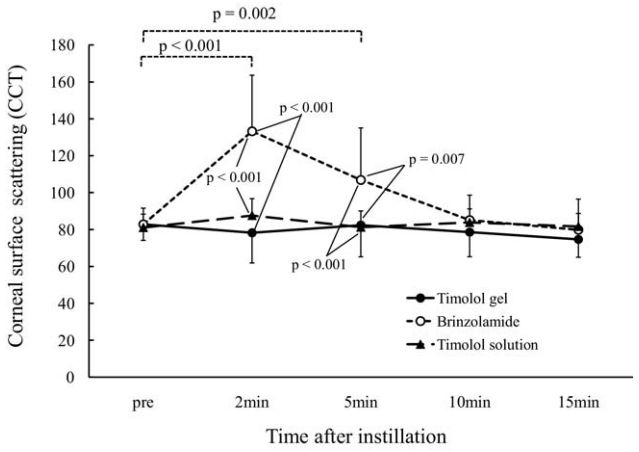

Figure 5. Time course of changes in corneal surface scattering. There was no significant change after instillation of timolol gel-forming solution ($P = 0.320$, repeated-measures ANOVA) and after instillation of standard timolol solution ($P = 0.073$), but a significant change was noted after instillation of brinzolamide ($P<0.001$). Multiple comparison analysis revealed that corneal surface scattering increased at 2 and 5 minutes after instillation of brinzolamide compared with the baseline ($P<0.001$ and $P = 0.002$, respectively, Dunnett test). On comparison of the 3 drugs, there were significant differences in corneal surface scattering at 2 and 5 minutes after instillation (both $P<0.001$, 1-way ANOVA). Bonferroni's multiple comparison test showed significant differences between brinzolamide and standard timolol solution (both $P<0.001$ for 2 and 5 minutes) and between brinzolamide and timolol gel-forming solution ($P<0.001$ for 2 minutes and $P = 0.007$ for 5 minutes). Graphs are expressed as the mean ± standard deviation. CCT = computer-compatible tape units.

gel-forming solution and standard timolol solution ($P = 0.192$ for 2 minutes and $P = 0.873$ for 5 minutes) (Fig 5).

Discussion

As shown in the results, contrast sensitivity decreased immediately after instillation of timolol gel-forming solution and brinzolamide, and gradually recovered toward the pre-instillation level. A statistically significant decrease in contrast sensitivity was found up to 5 minutes after instillation. The time course of changes was similar between the 2 drugs. This means that both timolol gel-forming solution and brinzolamide temporarily reduce QOV. To the best of our knowledge, this is the first study to show the influence of antiglaucoma eyedrops on contrast sensitivity function. Shibuya et al[10] reported a mean duration of 4.5±7.3 minutes of subjective perception of blurred vision after instillation of timolol gel-forming solution. The reported duration of blurred vision corresponds to the changes in contrast sensitivity in our study. Although self-perception of blurred vision was not assessed in this study, we believe that the reduced contrast sensitivity is associated with transient blurring of vision after instillation of these drugs, as reported by some patients.

Several studies have demonstrated that contrast sensitivity correlates well with various abilities of daily living and specific tasks, such as reading speed,[42–44] mobility and walking speed,[45] driving performance,[46,47] and computer task accuracy.[48] Owsley et al[47] examined the impact of contrast sensitivity loss on motor vehicle collision in older drivers. The authors showed that a contrast sensitivity level <1.25 log units in a single eye was significantly associated with crash involvement (odds ratio = 2.70) and that a level <1.25 in both eyes was more strongly correlated with crash involvement (odds ratio= 5.78). In addition, West et al[43] showed that a contrast sensitivity of ≤1.40 log units was related to disability in reading speed in an aging population. Several studies have assessed contrast sensitivity function in patients with glaucoma. Essock et al[49] and Hawkins et al[50] showed that the mean log contrast sensitivity was 1.44 in patients with glaucoma. Szlyk et al[51] reported a mean log contrast sensitivity of 1.58±0.17 for better eyes and 1.38±0.28 for worse eyes in patients with glaucoma. Bose et al[52] reported a mean log contrast sensitivity of 1.39±0.38 in patients with normal-tension glaucoma. The current study found a mean decrease in contrast sensitivity 2 minutes after instillation of 0.15 log units from the baseline value in both timolol gel-forming solution and brinzolamide. When these eyedrops are instilled in patients with glaucoma, it is possible that the contrast sensitivity level falls below the critical level of 1.40 units for disability in reading or 1.25 for motor vehicle crash involvement, even if their baseline contrast sensitivity levels are above these critical levels. In view of these findings, patients with glaucoma should be advised to refrain from driving or other activities requiring good visual function immediately after instillation of these drugs.

In study 2, we examined 2 optical quality parameters, such as HOA and light scattering at the corneal surface, to explore responsible factors that reduce QOV. As a result, both timolol gel-forming solution and brinzolamide temporarily increased HOA after instillation, although standard timolol solution did not. However, the degree and duration were higher after instillation of timolol gel-forming solution than after instillation of brinzolamide. The significant increase in HOA continued for 2 minutes after instillation of brinzolamide, whereas it persisted for 5 minutes after instillation of timolol gel-forming solution. In contrast, corneal surface light scattering significantly increased until 5 minutes after instillation of brinzolamide, but not after instillation of timolol gel-forming solution and standard timolol solution. These findings may indicate that the reduction in contrast sensitivity after timolol gel-forming solution instillation is mainly attributed to the increase in HOA, whereas it is probably caused by both increases in HOA and light scattering after instillation of brinzolamide. Unfortunately, we have no data to evaluate the direct relationship between contrast sensitivity and optical quality parameters. Further studies are necessary to confirm this speculation.

These different mechanisms underlying contrast sensitivity reduction may be explained by the physiologic properties and dynamics of these drugs on the corneal surface. Gellan gum, which is contained in timolol gel-forming solution, instantly becomes a gel by reacting

with cations in the precorneal tear film.[10] Once the gel forms, the formulation is subsequently dispersed by the shearing action of the eyelids that fragments the gel, and the gel fragments are then cleared from the ocular surface through the nasolacrimal duct.[53] Greaves et al[53] examined the clearance rate of gellan gum from the ocular surface using a scintigraphic technique and reported that detectable quantities of gellan gum remained on the corneal surface or at the lower fornix for up to 100 minutes.[53] However, because clearance follows bi-exponential kinetics, there is a rapid clearance in the early phase after instillation.[53] In view of these findings, gellan gum on the ocular surface seems to affect tear regularity and stability for up to 5 minutes so that the optical quality of the eye and QOV are decreased, although small amounts of gel will still remain on the ocular surface thereafter.

However, brinzolamide ophthalmic suspension does not contain any gel-forming vehicles. Brinzolamide itself is a white powder with a molecular weight of 383.5, which is insoluble in water. Once the preparation is instilled, the white particles mix with tears and spread over the ocular surface. These white particles are considered to increase corneal surface light scattering. As these particles are drained from the ocular surface through the lacrimal passage, light scattering is likely to decrease with time. In our study, corneal surface scattering increased immediately after instillation, and then decreased gradually. Statistically significant increases were confirmed up to 5 minutes after instillation. Higher-order aberration also increased after instillation of brinzolamide, even though the HOA increases were smaller and shorter than those after administration of timolol gel-forming solution. Brinzolamide ophthalmic suspension also contains insoluble carboxyvinyl polymer. Tsukamoto et al[54] suggested that this ingredient is related to the occurrence of blurred vision. Such insoluble components may be associated with an uneven spreading of the precorneal tear film, leading to increases in HOA.

Study Limitations

First, subjects were different between the 2 studies. Thus, we could not directly assess the relationship between parameters, such as contrast sensitivity, HOA, and light scattering in the same population. In previous studies, the influence of HOA or light scattering on contrast sensitivity function has been evaluated in eyes with various conditions. Applegate et al[55] assessed eyes with various pathologic corneal conditions and reported that, regardless of the causes, eyes with increased wavefront aberration showed quantifiable decreases in contrast sensitivity. In normal human eyes, Oshika et al[56] reported that coma-like aberration of the eye significantly influenced contrast sensitivity function. Likewise, significant relationships between light scattering and contrast sensitivity function have been reported in various conditions, such as in eyes with cataracts,[28] posterior capsule opacification after cataract surgery,[57] post-penetrating keratoplasty,[58] and post-photorefractive keratoplasty.[59,60] However, it is unknown how the increases in HOA and light scattering influenced contrast sensitivity after instillation of antiglaucoma eyedrops used in this study. Further studies are needed to elucidate this point. Second, none of the subjects had lacrimal drainage system obstruction. The increases in HOA and light scattering intensity found in this study will be accelerated and prolonged if the drug is instilled in patients who have some trouble with the lacrimal passage, such as dacryostenosis or nasolacrimal duct obstruction. Ishioka et al[61] examined the ocular surface change after instillation of timolol gel-forming solution using a tear lipid layer interference camera (DR-1, Kowa, Nagoya, Japan) in normal eyes and eyes with punctal plugs. The authors reported that the gel formulation was clearly observed immediately after instillation and disappeared within 2 to 5 minutes in eyes without plugs, whereas the gel fragments were retained for 10 to 30 minutes and distributed unevenly on the cornea in eyes with punctal plugs.[61] The prevalence of nasolacrimal duct obstruction[62] and glaucoma[63–65] increases with age. Given the large population of the elderly with glaucoma, the influence of this drug on the optical quality of the eye and QOV should be examined in patients with lacrimal drainage system obstruction.

In conclusion, this study demonstrated a significant reduction in contrast sensitivity for approximately 5 minutes after instillation of timolol gel-forming solution and brinzolamide ophthalmic suspension. Both drugs significantly increased HOA, and the increases were higher and longer after instillation of timolol gel than after instillation of brinzolamide. Corneal surface light scattering increased only after instillation of brinzolamide. On the basis of the current results, the possible reduction in optical quality of the eye and QOV should be sufficiently explained to patients receiving such eyedrops, because glaucoma is a disease that generally requires lifelong treatment. In particular, patients may be advised to refrain from driving or other activities requiring good visual function immediately after the instillation. Finally, in developing new antiglaucoma eyedrops, the impact on QOV and optical quality of the eye should also be considered, although it is certain that neuroprotective effects and IOP-lowering effects are most important for solving the progressive visual field defect in patients with glaucoma.

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