Effect of Instillation of Eyedrops for Dry Eye on Optical Quality

Shizuka Koh,1 Naoyuki Maeda,1 Chikako Ikeda,1,2 Yoshihiro Takai,1,2 Hisataka Fujimoto,1 Yoshinori Oie,1 Takeshi Soma,1 Motokazu Tsujikawa,1 and Kohji Nishida1

1Department of Ophthalmology, Osaka University Graduate School of Medicine, Suita, Osaka, Japan
2Research and Development Division, Rohto, Kyoto, Japan

Correspondence: Shizuka Koh, Department of Ophthalmology, Osaka University Graduate School of Medicine, Room E7, 2-2 Yamadaoka, Suita, Osaka, 565-0871, Japan; skoh@ophthal.med.osaka-u.ac.jp.
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PURPOSE. To investigate the effects of viscosity and suspensibility of eyedrops for dry eye by evaluating an eyedrop with one of the solutions or no solution (0.3% sodium hyaluronate ophthalmic solution, 3% diquafosol ophthalmic solution, and 2% rebamipide ophthalmic suspension) on ocular higher-order aberrations (HOAs) and forward light scatter.

METHODS. We evaluated ocular HOAs and forward light scatter before and 1, 5, and 10 minutes after instillation of three eyedrops for dry eye in 15 healthy subjects. Saline served as the control. The HOAs were measured for a 4-mm pupil using a wavefront sensor. The obtained aberration data were analyzed in the central 4-mm diameter for total HOAs up to the sixth-order Zernike polynomials. Forward light scatter was quantified with a straylight meter.

RESULTS. A significant increase was seen in the HOAs 1 minute after instillation of the three eyedrops for dry eye: the HOAs recovered to the baseline level thereafter. When 0.3% sodium hyaluronate was compared with 2% rebamipide and 3% diquafosol, the HOAs increased significantly (P < 0.01 for both comparisons) immediately after instillation. A significant increase in forward light scatter occurred 1 minute after instillation of rebamipide suspension and returned to the preinstillation level 5 minutes after instillation. No significant changes in forward light scatter occurred after instillation of 3% diquafosol or 0.3% sodium hyaluronate.

CONCLUSIONS. Quantitative serial measurement of HOAs and forward light scatter showed that the temporal reduction in optical quality may be attributed mainly to increased HOAs after instillation of highly viscous 0.3% sodium hyaluronate ophthalmic solution and to increased forward light scatter after instillation of 2% rebamipide ophthalmic suspension in healthy subjects.

Keywords: dry eye, wavefront aberration, light scatter

Dry eye, one of the most common reasons patients seek ophthalmologic evaluations, is characterized by ocular surface discomfort, redness, light sensitivity, and variable visual disturbances.3 Artificial tears and tear retention agents have been used to lubricate the ocular surface and improve irritation symptoms. Use of these eyedrops is expected to provide a smooth refractive surface and reduce optical aberrations associated with unstable, impaired tear film. Several studies have reported the effect of artificial tears, including tear retention agents, on contrast sensitivity2–5 or corneal topographic data6–11 in normal and dry eyes. Moreover, some studies that measured wavefront aberrations have reported a temporal optical effect of these eyedrops on corneal or ocular higher-order aberrations (HOAs) in normal and dry eyes.12–16 Some eyedrops have higher concentrations of viscous agents to increase the tear retention time. Sodium hyaluronate ophthalmic solution has been used widely to treat dry eye. Owing to its viscoelastic rheology, high-viscosity sodium hyaluronate can retain large quantities of water and resist dehydration.17–19 However, the resultant blurred vision is a drawback of agents with high viscosity.20 Previous studies used contrast sensitivity or wavefront aberration measurements to quantify the short-term blurring of vision caused by viscous eyedrops.5,16,21

Two new topical pharmacologic agents recently have become commercially available for treating dry eye in Japan. Diquafosol ophthalmic solution stimulates aqueous secretion and mucous secretion directly on the ocular surface. Rebamipide ophthalmic suspension also stimulates mucous secretion. Several recent studies have reported the clinical efficacy of both drugs for dry eye22–28; however, some patients have complained of temporary visual disturbances after rebamipide,28 presumably because of the drug’s suspensibility. Despite the widespread increased use of both drugs in clinical practice, little is known about the effect of these drugs on optical quality.

Recent technologic advances have enabled quantitative measurement of forward light scatter29–31 and a number of studies have reported forward light scatter in cataractous eyes, pseudophakic eyes, or eyes that underwent corneal surgeries. Previous study has reported the effects of lubricating eyedrops on forward light scatter.32 Because patients with dry eye generally require instillation of eyedrops several times a day, the effects of viscosity and suspensibility of ophthalmic drugs are of interest. To the best of our knowledge, no studies have evaluated these effects of eyedrops for dry eye.

In the current study, we quantified the effects of viscosity and suspensibility of eyedrops for dry eye by evaluating
eyedrops with one of these solutions or no solution (sodium hyaluronate ophthalmic solution, diquafosol ophthalmic solution, and rebamipide ophthalmic suspension) on ocular HOAs and forward light scatter.

METHODS

The institutional review board of Osaka University Hospital approved this study. The research adhered to the tenets of the Declaration of Helsinki. All subjects provided informed consent after they received an explanation of the nature and possible consequences of the study.

Fifteen eyes of 15 healthy volunteers (6 men, 9 women; average age, 32.0 ± 5.7 years) who had no ocular diseases except refractive errors were included. No subject wore contact lenses or had undergone a previous ocular surgery, and none used eyedrops or were taking a systemic medicine. All eyes had a best spectacle-corrected visual acuity of 20/20 or better. The average Schirmer I test result was 28.3 ± 6.3 mm, and slit-lamp examinations showed no fluorescein staining on the ocular surface. The mean tear film break-up time (BUT) was 7.5 ± 1.7 seconds. To avoid the effect of other tests on the measurement of optical quality, tear function tests and slit-lamp examinations were conducted on a separate day before the measurements.

Tested Eyedrops

We tested an isotonic borate-buffered saline (Soft Santear; Santen Pharmaceutical Co., Osaka, Japan) as the control and three different dry-eye drops including 0.3% sodium hyaluronate ophthalmic solution (0.3% Hyalein; Santen Pharmaceutical Co.), 3% diquafosol ophthalmic solution (3% Diquas; Santen Pharmaceutical Co.), and 2% rebamipide ophthalmic suspension (preservative-free) (Mucosta Ophthalmic Suspension UD2; Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan). Because the manufacturers’ disclosed information about viscosity and suspensibility differ according to the measurement conditions, we measured the two parameters of the four eyedrops under the same conditions. The viscosities were measured at 20°C using the E-type Viscometer (TVE-20; Tokyo Keiki Co., Tokyo, Japan) (Table). The suspensibility values of the samples were determined using a turbidimeter (NDH-300A; Nippon Denshoku Industries Co., Ltd., Tokyo, Japan).

Experimental Protocol

Ocular wavefront aberrations were measured using a custom-developed Hartmann-Shack wavefront aberrometer (Topcon Corp., Tokyo, Japan) in a dark room through a natural pupil without pupil dilation. The wavefront data were analyzed quantitatively in the central 4-mm diameter up to the sixth order by expanding the set of Zernike polynomials. The magnitudes of the coefficients of the Zernike polynomials are represented as the root mean square (RMS) expressed in micrometers. The RMS was calculated for second-, third-, fourth-, fifth-, sixth-, and total HOAs in the central 4-mm diameter. For example, the third order has four terms that represent coma and trefoil astigmatism. The fourth order has five terms, including the spherical aberration. Spectacles can correct only the second-order aberrations. Third- and greater-order aberrations are identified as HOAs. The RMS of third-order and fifth-order Zernike coefficients was used to represent coma-like aberrations, and the RMS of fourth-order and sixth-order Zernike coefficients was used to represent spherical-like aberrations. The total HOAs were calculated as the RMS of third-, fourth-, fifth-, and sixth-order Zernike coefficients.

Forward light scatter was evaluated quantitatively using the C-Quant Straylight Meter (Oculus GmbH, Wetzlar, Germany), which measures the level of intraocular straylight based on the compensation-comparison method. The principles, technique, and reproducibility of the device have been described.

Briefly, the eye to be tested was positioned a minimal distance from the eyepiece, and the subjects performed a forced-choice comparison of two half-fields in the center of the field to determine which one flickered more strongly. A psychometric response curve was computed from the subjects’ responses. The untested eye was patched during the measurement. The amount of straylight was expressed as the logarithm of the straylight parameters (log [s]); higher values indicated more straylight and more glare sensitivity. In the straylight meter, a reliability parameter, specified as the expected standard deviation (ESD), can be designed that predicts the accuracy of an individual measurement. The quality (Q) of each measurement also can be evaluated. In the current study, the ESD and Q values were 0.06 ± 0.01 and 1.62 ± 0.33, respectively. The measurement is considered reliable when the ESD is below 0.08 and the Q exceeds 1.0.

To measure wavefront and forward light scatter, subjects randomly received one drop of a drug, and the examinations were performed before and 1, 5, and 10 minutes after drug instillation. Four different eyedrops were assessed on four different days, and wavefront and light scatter measurements were performed on separate days. Thus, the measurements were performed eight times for each subject.

The data were analyzed using statistical analysis software SigmaPlot 12 (Systat Software, Inc., Chicago, IL). The Friedman repeated-measures ANOVA on ranks test was used to assess the time course of each parameter over 10 minutes. The appropriate post hoc Dunnett’s correction for multiple comparisons was used. The Kruskal-Wallis test was performed to compare each parameter among the drugs at each time point. The appropriate post hoc Tukey correction for multiple comparisons was used in this comparison. P less than 0.05 was considered significant for all analyses.

RESULTS

The time courses in HOAs are shown in Figures 1 to 3. Instillation of all three dry-eye drops (four drugs except saline) significantly (P < 0.001, for all comparisons) changed the coma-like aberrations, spherical-like aberrations, and total HOAs; no significant (P = 0.724, 0.114, and 0.608, respectively) changes were associated with saline. All HOA components increased immediately after instillation of the three dry-eye drops and then returned to the preinstillation level. Compared with baseline, significant (P < 0.001 for all comparisons) increases in coma-like aberrations, spherical-like aberrations, and total HOAs occurred immediately after instillation of sodium hyaluronate. Likewise, significant increases in coma-like aberrations, spherical-like aberrations, and total HOAs occurred immediately after instillation of diquafosol and rebamipide (P = 0.054, P = 0.003, P = 0.036, respectively, for diquafosol, and P = 0.003, P < 0.001, P =
0.003, respectively, for rebamipide). Five and 10 minutes after instillation, there were no significant increases in the HOA components. Comparison of the four drugs showed that coma-like aberrations, spherical-like aberrations, and total HOAs immediately after instillation of sodium hyaluronate had significantly ($P < 0.001$ for all comparisons) higher values than those of the other three drugs. At 5 and 10 minutes after instillation, there were no significant differences in the HOA components among the drugs.

The time courses in forward light scatter are shown in Figure 4. There were significant ($P < 0.001$) changes after instillation of rebamipide eyedrops; no significant ($P = 0.060, 0.504, \text{and} 0.346, \text{respectively}$) changes were found with instillation of diquafosol, sodium hyaluronate, or saline.

**Figure 1.** The average time course in coma-like aberrations for all subjects. The error bars represent the SDs of the subjects. Pre, preinstillation.

**Figure 2.** The average time course in spherical-like aberrations for all subjects. The error bars represent the SDs of the subjects.
Forward light scatter significantly ($P < 0.001$) increased immediately after instillation of rebamipide compared with the baseline values and then returned to the preinstillation level. Five and 10 minutes after instillation of rebamipide, there were no significant increases in forward light scatter. Comparison of the four drugs showed that forward light scatter immediately after instillation of rebamipide was significantly ($P < 0.001$ for all comparisons) greater than with the other three drugs. Five and 10 minutes after instillation, there were no significant differences among the drugs.

**DISCUSSION**

Aberrations and scattering are the main factors in the degradation of optical quality in human eyes. The irregularity
of the refractive surface causes increased HOAs, and light scatter can be induced by surgery, opacity, or trauma. The current study quantitatively showed marked increases in HOAs immediately after instillation of highly viscous 0.3% sodium hyaluronate ophthalmic solution and marked increases in forward light scatter immediately after instillation of 2% rebamipide ophthalmic suspension. Both temporal changes recovered to the baseline level 5 minutes after instillation.

Increases in HOAs occurred 1 minute after instillation of dry-eye drops except for saline. These results agreed with previous studies that reported reduced contrast sensitivity or increased corneal irregularity and HOAs immediately after instillation of artificial eyedrops.\textsuperscript{3,6,10,16} Ishioka et al.\textsuperscript{21} reported that functional visual acuity and corneal regularity decreased immediately after instillation of 0.3% sodium hyaluronate and returned to the preinstillation level 5 minutes after instillation. The investigators reported no such changes with instillation of 0.1% sodium hyaluronate. In the current study, similar changes in wavefront data were found with 0.3% sodium hyaluronate and the increases in HOAs with instillation of 0.3% sodium hyaluronate were significantly greater than with other eyedrops immediately after instillation. The Table shows that the high viscosity of 0.3% sodium hyaluronate might be considered a major contribution to the markedly increased HOAs immediately after instillation. Berger et al.\textsuperscript{16} also reported that the more viscous artificial eyedrops yielded significantly higher HOAs than those with lower viscosity. Interestingly, Shimamura et al.,\textsuperscript{8} who used corneal pachymetry maps, reported that 0.3% sodium hyaluronate provided even distribution of the tear film compared with saline, immediately after instillation. Because even distribution of tear film can result in a smooth refractive surface, which seems to contradict previous results\textsuperscript{16,21} of worsening corneal regularity or ocular HOAs, including the current results, further study should investigate the relationships between tear film thickness and HOAs after instillation of viscous artificial eyedrops such as 0.3% sodium hyaluronate.

Recently, the therapeutic effects of diquafosol ophthalmic solution and rebamipide ophthalmic suspension on HOAs for the short BUT-type of dry eye have been reported\textsuperscript{25,28}; however, the short-term effects of these eyedrops on optical quality are unknown. We previously reported worsening corneal irregularity and HOAs immediately after instillation of artificial eyedrops.\textsuperscript{3,6,10,16} In the current study, immediately after instillation, increased HOAs developed with both drugs, and remarkable increases in forward light scatter occurred only with rebamipide ophthalmic suspension, which returned to the preinstillation level 5 minutes after instillation. Measurement of wavefront aberrations with a wavefront sensor is a method that is commonly used to measure HOAs of the entire eye and evaluate optical quality. However, the main drawback is the failure to measure light scatter.\textsuperscript{57} As shown in the current study, a temporal reduction in optical quality after rebamipide instillation was detected only by measuring the forward light scatter. Previously, Veraart and van den Berg\textsuperscript{52} studied the effects of eight different artificial tears on optical quality using a starlight meter in healthy eyes and found no significant changes in intraocular light scatter. In a future study, it would be of interest to determine the effects of the dry eye ophthalmic solutions and suspension tested in the current study on light scatter in patients with dry eye.

Hiraoaka et al.\textsuperscript{58} reported that increases in backward light scatter persisted longer than 5 minutes after instillation of brinzolamide 1% ophthalmic suspension (Azopt; Alcon Laboratories, Inc., Fort Worth, TX), whereas in the current study, significant increases in forward light scatter were seen only immediately after instillation of rebamipide suspension. The measured suspensibility of brinzolamide 1% suspension under the same conditions as for rebamipide (Table) was over 100, like rebamipide; however, the viscosity was over 2000. Despite the difference between forward and backward light scatter, the markedly greater viscosity of brinzolamide compared with that of rebamipide may prolong the retention of white particles on the ocular surface and account for the difference in the duration of the increased light scatter.

Interestingly, although the viscosity and suspensibility of diquafosol and saline were similar (Table), the increases in the HOAs after instillation were found only for diquafosol. Based on animal studies, 3% diquafosol increased the tear meniscus dimension 15 minutes after instillation in normal cats\textsuperscript{39} and the Schirmer test score 15 minutes after instillation in normal rabbits.\textsuperscript{40} In addition, 3% diquafosol increased the Schirmer test score 10 minutes after instillation in a rat dry eye model.\textsuperscript{41} Although we could not determine if the tear volume increased due to aqueous secretion after instillation of diquafosol in healthy subjects in the current study, aqueous secretion might be involved. Moreover, the difference in the pH and osmolarity of eyedrops may have an effect.\textsuperscript{42}

Because dry eye is a chronic, symptomatic ocular surface disease, patients with dry eye generally require lifelong use of eyedrops. The findings in the current study would help improve drug compliance in patients treated with rebamipide or 0.3% sodium hyaluronate. However, the fluid dynamics of these eyedrops on the ocular surface in dry eyes might differ from that in normal eyes, since there is delayed tear clearance resulting from decreased tear volume; some blockage in the lacrimal pathway or lacrimal pump failure might be possible in dry eye. Further studies of patients with dry eye would be helpful to understand the actual conditions during eyedrop instillation.

In the current study, we did not perform subjective visual assessments such as contrast sensitivity or use a visual analogue scale–based questionnaire. It would have been interesting to investigate the relationship between HOAs or forward light scatter and those parameters. Moreover, the current enrolled subjects were young and healthy with no corneal diseases or cataract; however, dry eye is common among all age groups, including middle-aged and elderly people. In addition, the liquid viscosity tends to decrease with increasing temperatures, although it has been reported that the temperature dependence of the hyaluronate viscosity is suppressed partly with the increasing concentration of the polymer.\textsuperscript{35,44} Because the measurements were performed eight times for each subject on separate days in the current study, it may be possible that the viscosity of the eyedrops might have been affected by the temperature and humidity during each measurement condition, which in turn affected the results of the measurements of the HOAs and light scatter.

In conclusion, objective assessment of HOAs and forward light scatter quantitatively showed the time course in optical quality associated with instillation of eyedrops for dry eye. The current study of normal eyes showed that instillation of highly viscous 0.3% sodium hyaluronate ophthalmic solution may contribute to increased HOAs, and instillation of 2% rebamipide ophthalmic suspension may contribute to increased forward light scatter. Properties such as the viscosity and suspensibility of eyedrops affect the optical quality.

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