

# Time course of changes in ocular wavefront aberration after administration of eye ointment

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## Abstract

**Purpose** To investigate the influence of an eye ointment on ocular aberration.

**Design** Prospective, comparative study.

**Methods** In 10 normal volunteers, ocular aberration was assessed before and 5, 30 min, 1, 2, 3, 6, and 12 h after administration of ofloxacin eye ointment. Ocular aberration was sequentially measured over a period of 10 s, and the root mean square (RMS) of the second-, third-, fourth-, and total higher-order aberrations (HOAs) were determined. From the sequential changes in total HOAs during 10 s, the fluctuation index (FI) and stability index (SI) were calculated. The obtained data were compared with those of another 17 normal volunteers who received timolol maleate gel-forming ophthalmic solution.

**Results** No significant changes in second-order RMS were observed after administration of the ointment. HOAs such as third-, fourth-, and total higher-order RMS significantly changed during the study period ( $P < 0.05$ , repeated-measures analysis of variance). The RMS of each HOA component significantly increased 5 min after administration compared with the baseline values ( $P < 0.05$ , Dunnett test). FI also increased significantly 5 min after administration ( $P < 0.05$ ), but SI did not change significantly. When compared with the results of the gel-forming solution group, HOAs and FI showed significantly higher values at several time points during 6 h after application ( $P < 0.05$ , Mann–Whitney *U*-test).

**Conclusions** Administration of eye ointment significantly degrades optical quality of the eye by increasing and oscillating HOAs. These changes were more pronounced than those after instillation of gel-forming

**ophthalmic solution for at least several hours.**

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**Keywords:** higher-order aberrations; eye ointment; optical quality of the eye; tear film; blurred vision

## Introduction

Eye ointments, which commonly include petrolatum and mineral oil with or without hydrophilic lipids such as lanolin or polyethylene glycols as its base,<sup>1</sup> ensure superior drug bioavailability by increasing contact time with the eye, minimizing dilution by tears, and resisting nasolacrimal drainage.<sup>2,3</sup> They are widely used in clinical practice for various purposes. Some ointments contain antibiotics to treat or prevent infections, while others provide lubrication to treat or prevent exposure keratopathy. In many facilities, application of antibiotic ointments into the conjunctival fornix at the completion of surgery is still routinely practiced.<sup>4</sup> It is also standard to administer antibiotic ointments to eyelid margin to reduce bacterial colonization preoperatively.<sup>5</sup> In the treatment of blepharitis or eyelid infection, the use of antibiotic ointments rather than eyedrops is often required.<sup>6,7</sup> It is also known that some drugs such as fluorometholone,<sup>8</sup> chloramphenicol,<sup>9</sup> and tetracycline<sup>10</sup> achieve higher aqueous levels when administered as ointments than when given as eyedrops. Furthermore, eye ointments have also been employed for the treatment of keratoconjunctivitis sicca and dry eye.<sup>11–13</sup> As described above, eye ointment is still an essential treatment modality in clinical practice.

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However, the use of eye ointment is often accompanied by visual impairment for 10–15 min,<sup>6</sup> and the bulk application can cause lengthy blurred vision up to several hours, resulting in decreased patient satisfaction and restriction of daily activities.<sup>11,14</sup> Especially when an ointment is applied to both eyes, patients commonly become handicapped by blurred vision.<sup>15</sup> Such visual deterioration is considered to result from an irregular spreading behavior of ointment on the ocular surface.<sup>16,17</sup>

Acyclovir is one of the most commonly used antiviral drugs, but it cannot be formulated as eyedrops because of its poor water solubility. Therefore, only the ointment formulation is available and used for the treatment of herpes simplex keratitis, blepharoconjunctivitis, and iridocyclitis.<sup>18,19</sup> However, it requires the five times daily dosing regimen to keep an effective drug level because of its very short half-life, and consequently patients often find it difficult to follow the prescribed treatment schedule due to the long-lasting blurred vision after application.<sup>20</sup>

Although it is well accepted that eye ointments severely affect visual performance, as mentioned above, little is known about their influence on optical quality of the eye. Given widespread application of eye ointments from children to the elderly, it is crucial to analyze the optical impact and to inform patients and practitioners of such effect. Wavefront analysis is a method designed to measure refractive errors in a more accurate way. By using wavefront sensors, ocular optical errors are assessed from the viewpoint of the wave property of light as wavefront aberrations, and it is possible to obtain information regarding not only lower-order aberrations (defocus and astigmatism), but also higher-order aberrations (HOAs) that were not measurable before the introduction of this technology. Both lower- and higher-order wavefront aberrations determine the quality of images formed on the retina. This technique enables us to understand ocular optical quality in detail. Therefore, we objectively and quantitatively assessed the influence of an eye ointment on ocular optical quality by evaluating the time course of changes in ocular wavefront aberration after administration. In Asia, ofloxacin eye ointment is one of the most frequently used eye ointments,<sup>11,21,22</sup> so it was employed as a representative drug in this study.

Recently, some gel-forming ophthalmic solutions, which allow greater ocular penetration by prolonging ocular retention and increasing corneal contact time, are available in clinical practice. It is well known that this kind of eyedrops also cause transient visual blurring after administration.<sup>23</sup> We have previously investigated the impact of a gel-forming solution on ocular wavefront aberration and found significant increases in HOAs after administration for ~5 min.<sup>24</sup> In this study, comparison

between the present and the previous results was also conducted.

## Subjects and methods

One eye of each normal volunteer (total of 10 participants, 4 males and 6 females;  $35.5 \pm 12.7$  years (mean  $\pm$  SD)) without systemic and ocular diseases (except for refractive errors) was enrolled in this study. Contact lens users were not included. They did not have any history of eye surgery or trauma, symptoms of dry eye, and regular use of eyedrops. At the time of enrollment, all subjects had best-corrected visual acuity of 20/20 or better. The study adhered to the tenets of the Declaration of Helsinki and was approved by the institutional review board of Tsukuba University Hospital. Informed consent was obtained from all study participants after the nature and possible consequences of the study had been explained to them in detail.

Only the right eye was used for the measurements because it has been shown that aberration patterns are generally symmetric between left and right eyes of a same subject.<sup>25</sup> At baseline, ocular wavefront aberration was assessed in a dark room through a natural pupil without the use of dilating drugs, and serial measurements were performed using the newly developed Hartmann-Shack wavefront aberrometer (KR-1W, Topcon, Corp., Tokyo, Japan) equipped with an automated function of measuring and recording sequential wavefront aberrations every second. This system has been described in detail elsewhere.<sup>26</sup> Ten serial images were obtained at 1-sec intervals from 1 to 10 s following a blink. The subjects were instructed to keep their eyelids open during the image capture. Subsequently, we applied 0.05 g of 0.3% ofloxacin eye ointment (Tarivid, Santen Pharmaceutical, Osaka, Japan) along a length of 1 cm on a glass rod measuring by a calibrated grid and then placed the ointment in the inferior cul-de-sac. The ointment consists of 0.3% ofloxacin, liquid paraffin, white petrolatum, and purified lanolin as its base. The eyes were then closed for 30 s and allowed to blink naturally. The same measurements were repeated 5, 30 min and 1, 2, 3, 6, and 12 h after the administration. Subjects were instructed not to wipe their eyelid margins throughout the study period. All measurements were conducted on the same day at Tsukuba University Hospital in a room in which the temperature was maintained at  $23.4 \pm 1.2$  °C and the humidity was  $52.1 \pm 1.7$ %.

The acquired data sets were expanded with the normalized Zernike polynomials. From the Zernike coefficients, the root mean square (RMS) was calculated for second-, third-, fourth-, and total HOAs in the central 4-mm diameter. The second-order aberration

corresponds to conventional refractive error (sphere and cylinder) that can be corrected by spherocylindrical lenses, whereas the third- and higher-order aberrations cannot. Therefore, third- and greater order aberrations are identified as HOAs. The RMS of third-order Zernike coefficients was used to represent coma-like aberration, and the RMS of fourth-order Zernike coefficients was used to denote spherical-like aberrations. Total HOAs were calculated as the RMS of third- and fourth-order Zernike coefficients.

According to the study of Koh *et al*,<sup>26</sup> two quantitative indices such as fluctuation index (FI) and stability index (SI) of the total HOAs were calculated from the sequential changes in ocular aberrations over time. The FI was defined as the standard deviation of the total HOAs obtained during the serial measurements for 10 s, which reflects the fluctuations in HOAs during the measurements. SI was calculated as the slope of the linear regression line of the total HOAs obtained, which represents the trend of the sequential changes in HOAs during the measurement.

The obtained data for 10 s (10 serial measurements) were averaged for each eye and analyzed by using repeated-measures analysis of variance (ANOVA) to assess the time course of changes in each aberration over 12 h. If significant differences 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, the obtained data were compared with those from an early study that investigated the influence of 0.5% timolol maleate gel-forming solution (Timoptol XE, Banyu Pharmaceutical Co., Ltd, Tokyo, Japan) on ocular wavefront aberration in 17 normal volunteers.<sup>24</sup> Intergroup comparisons were done by the Mann-Whitney *U*-test.  $P < 0.05$  was considered significant. All statistical analyses were performed using SPSS version 15.0J software (SPSS Inc., Chicago, IL, USA).

## Results

The eye ointment caused no significant time course of changes in second-order RMS ( $P = 0.737$ , repeated-measures ANOVA). HOAs such as third-, fourth-, and total higher-order RMS significantly changed during the study period ( $P = 0.002$ ,  $P = 0.045$ , and  $P = 0.006$ , respectively). Multiple comparison analysis revealed that the RMS of each HOA component significantly increased 5 min after administration of eye ointment compared with the baseline values ( $P < 0.001$  for third-,  $P = 0.037$  for fourth-, and  $P = 0.001$  for total higher-order RMS, Dunnett *post-hoc* test). All aberrations gradually returned to the preadministration level thereafter, but some fluctuations were observed (Figure 1).

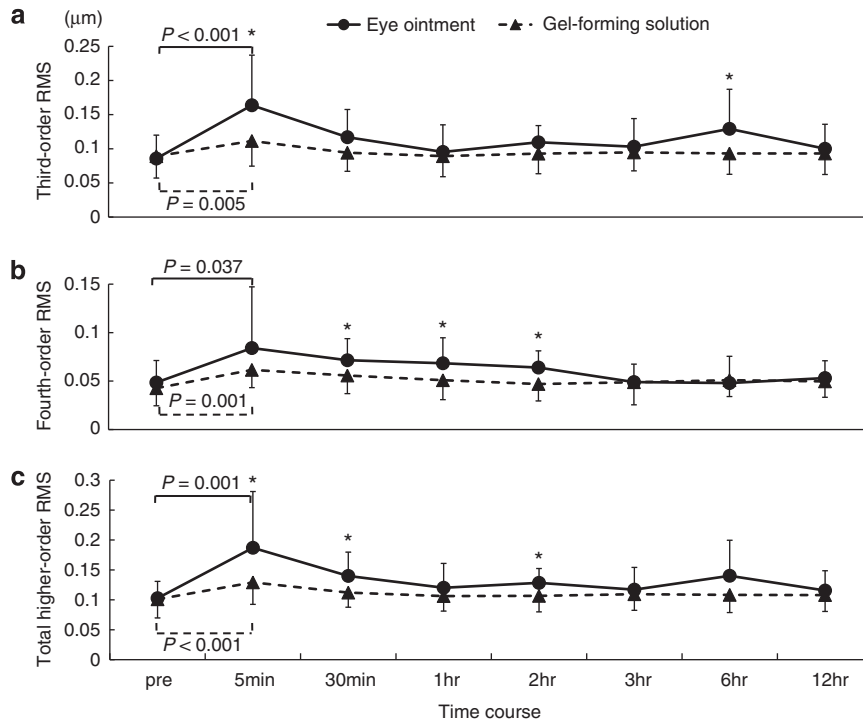
There was a significant time course of changes in FI during the 12-h study period after administration of eye ointment ( $P = 0.003$ , repeated-measures ANOVA). FI significantly increased 5 min after administration ( $P = 0.002$ , Dunnett *post-hoc* test), and returned toward the preadministration level thereafter (Figure 2). No significant changes were observed in SI over the study period after administration of eye ointment ( $P = 0.807$ , repeated-measures ANOVA).

Moreover, we compared the present results with those of the previous study using timolol gel-forming solution.<sup>24</sup> There were no significant differences between the two studies in terms of age, sex, Schirmer value, and breakup time (Table 1). There were no significant differences in second-order RMS between the two study groups over the study period ( $P = 0.471$ – $0.542$ , Mann-Whitney *U*-test). As for HOAs, significant differences in third-order RMS were found between the two groups at 5 min ( $P = 0.020$ ) and 6 h ( $P = 0.043$ ) following application (Figure 1). There were significant differences in fourth-order RMS between the two groups at 30 min ( $P = 0.040$ ), 1 h ( $P = 0.049$ ), and 2 h following application ( $P = 0.022$ ) (Figure 1). There were significant differences in total higher-order RMS between the two groups at 5 min ( $P = 0.031$ ), 30 min ( $P = 0.032$ ), and 2 h ( $P = 0.044$ ) following application (Figure 1). Significant differences in FI between the groups were also observed at 5 min ( $P = 0.039$ ), 30 min ( $P = 0.029$ ), and 2 h ( $P = 0.045$ ), and 3 h ( $P = 0.029$ ) following application (Figure 2). There were no significant differences in SI between the two groups over the study period ( $P = 0.274$ – $0.789$ ).

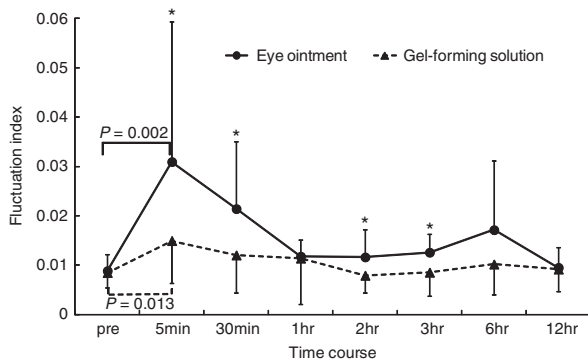
Time courses of changes in color-coded maps of HOAs and simulated retinal images from a representative case with gel-forming solution *vs* eye ointment are shown in Figure 3.

## Discussion

Tear film is the most anterior refractive surface of the eye and an essential optical element, of which stability and regularity are necessary to maintain the ocular optical quality.<sup>27</sup> Any local changes in tear film thickness and smoothness can affect optical aberrations.<sup>28,29</sup> So far, numerous studies have demonstrated that increased aberrations resulting from tear film instability deteriorate image quality.<sup>28–30</sup> Maintenance of an intact and smooth tear film is thus required for achieving high-quality retinal images.<sup>29</sup> In recent years, increasing attention has been focused on the sequential changes in the optical quality of the eye associated with tear film dynamics, because the deterioration of optical quality is not a static but dynamic phenomenon. Several studies have investigated the influence of tear film dynamics on sequential wavefront aberrations in dry eyes and normal



**Figure 1** Time course of changes in (a) third-, (b) fourth-, and (c) total higher-order RMS after administration of eye ointment and gel-forming solution. Significant changes were observed in third-, fourth-, and total higher-order RMS at 5 min after administration of gel compared with baseline values. There were additional significant differences in (b) fourth-order RMS at 30 min, 1, and 2 h, and in (c) total higher-order RMS at 30 min and 2 h after application (\* $P < 0.05$ , Mann-Whitney  $U$ -test). Graphs are expressed as the mean  $\pm$  SD.



**Figure 2** Time course of changes in FI after administration of eye ointment and gel-forming solution. FI significantly increased 5 min after administration in both groups. Significant differences in FI between the groups were observed at 5 min, 30 min, and 2 and 3 h after application (\* $P < 0.05$ , Mann-Whitney  $U$ -test). Graphs are expressed as the mean  $\pm$  SD.

eyes.<sup>26,31,32</sup> Nowadays, wavefront sensing has been recognized as a practical objective method for evaluating sequential changes in optical quality of the eye. Thus, in the present study, we examined the sequential changes in ocular aberrations with the wavefront aberrometer to comprehend the detailed influence of eye ointment on ocular optical quality.

Petrolatum–mineral oil ointments, which can provide higher and more sustained drug concentrations in the aqueous humour compared with solutions, have been widely used where a sustained effect is required.<sup>16</sup> Ofloxacin eye ointment, which consists of 0.3% ofloxacin, white petrolatum, mineral oil (purified lanolin), and lipid paraffin, is one of the representatives of petrolatum–mineral oil ointments. In addition, it is a nonpreserved antibiotic ointment and one of the most frequently used eye ointments in Asia.<sup>11,21,22</sup> Therefore, we selected this preparation as a representative ointment in this study.

Wavefront aberration, which is the distance between an actual wavefront and an ideal ‘reference’ wavefront centered on the ideal image point, consists of lower-order (second order) aberrations and HOAs. As HOAs cannot be corrected by spectacles with spherocylindrical lenses, it is important to evaluate HOAs when we consider the optical quality of the eye. There are two major aberrations (coma-like and spherical-like aberrations) in HOAs. Coma-like aberrations are asymmetric; that is, similar optical effects do not occur on opposing sides of the eye. Such asymmetric aberrations presumably arise from the various small tilts, decentrations, and other asymmetries of the components of the eye. On the other hand, spherical-like aberrations are symmetric; similar

**Table 1** Baseline characteristics of subjects in the eye ointment and gel-forming solution groups

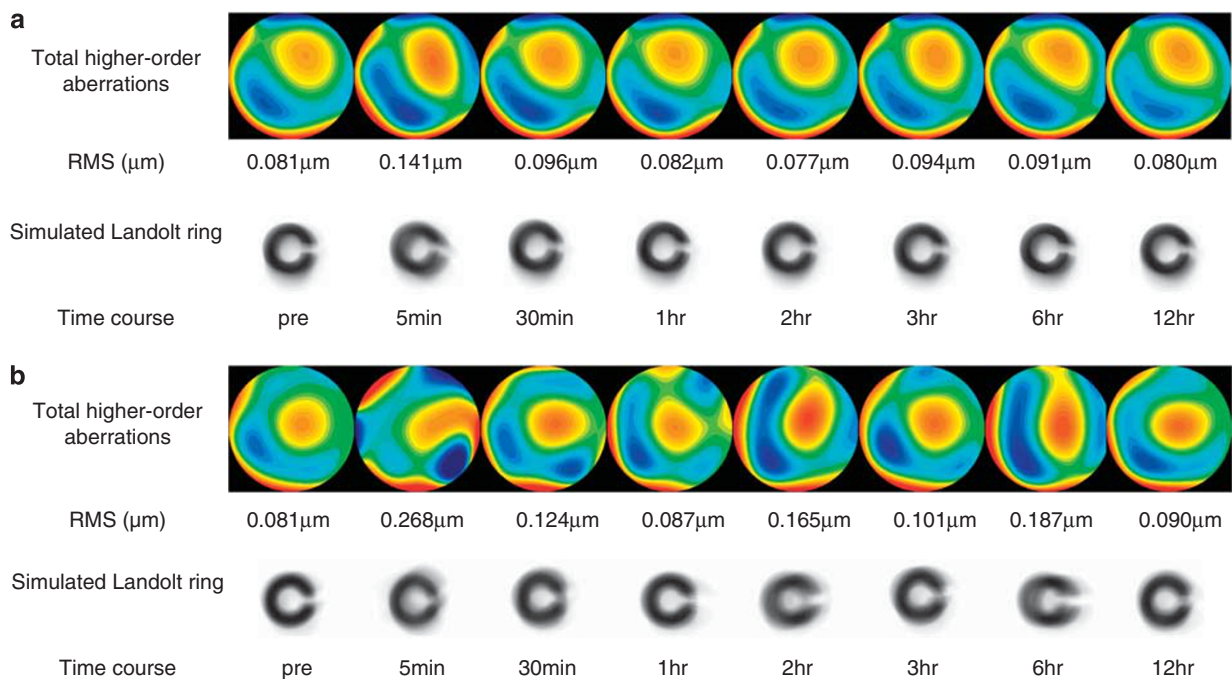
	Eye ointment group (n = 10)	Gel-forming solution group (n = 17)	P-value
Age (years)	35.5 ± 12.7	37.4 ± 15.4	0.841 <sup>a</sup>
Sex	Male: 4, Female: 6	Male: 10, Female: 7	0.5746 <sup>b</sup>
Schirmer test (mm)	34.3 ± 1.6	31.1 ± 7.6	0.282 <sup>a</sup>
Breakup time (in seconds)	9.8 ± 0.4	9.1 ± 1.3	0.186 <sup>a</sup>

Data are expressed as the mean ± SD.

No significant intergroup differences were observed at baseline in age, sex, Schirmer value, and breakup time.

<sup>a</sup>Mann-Whitney *U*-test.

<sup>b</sup>Chi-square test.



**Figure 3** Time courses of changes in color-coded maps of higher-order aberrations and simulated retinal images from a representative case with gel-forming solution (a) *vs* eye ointment (b). (a) At 5 min after administration of gel-forming solution, increases in the cooler color in the inferotemporal portion and the warmer color in the superonasal portion were found in the color-coded map. A blurry image of the simulated Landolt ring (optotype with log MAR value 0) was also observed. These changes improved thereafter without remarkable fluctuations. (b) In addition to increases in both cooler and warmer colors, the pattern of the color-coded map greatly changed at 5 min after administration of eye ointment. A blurry image of the simulated Landolt ring was also observed. Although these changes gradually improved until 1 h after the administration, they deteriorated again and fluctuated over the observation period.

optical effects occur on opposing sides of the eye. Total HOAs are the sum of coma-like and spherical-like aberrations. As shown in the results, all HOAs, such as coma-like, spherical-like, and total HOAs, increased significantly 5 min after administration, and then gradually returned to the baseline levels, whereas there were no significant changes in the second-order aberration throughout the study period. SI did not change significantly over the study period, whereas FI showed a transient increase 5 min after administration. The trend of each HOA component was similar to that

after administration of timolol gel-forming solution. When compared between the study groups at each time point, however, the mean RMS of each HOA component is almost always higher in the eye ointment group than in the gel-forming solution group, and statistically significant differences were observed in several time points (5 min and 6 h after application for coma-like aberration, 30 min and 1, 2 h after application for spherical-like aberration, and 5, 30 min and 2 h after application for total HOAs). Although the time points which showed significant differences were somewhat

different among the HOA components, these results imply that HOAs were considerably influenced by the administration of eye ointment for at least several hours. FI was also higher in the eye ointment group than in the gel-forming solution group at 5, 30 min, and 2, 3 h after application. This means that HOAs fluctuated more and were unstable during several hours after administration of the eye ointment compared with the gel-forming solution. In addition, increases in coma-like aberration were more outstanding than those in spherical-like aberration in the present study, although both of them increased. This indicates that the eye ointment tends to cause asymmetrical changes rather than symmetric changes in HOAs. To the best of our knowledge, this is the first study to elucidate the influence of eye ointment on ocular wavefront aberration.

Timolol gel-forming solution is also known to cause transient blurred vision.<sup>23</sup> The preparation contains gellan gum that instantly becomes gel by reacting with cations in the precorneal tear film, although it is liquid at room temperature.<sup>23</sup> Once the gel is formed, the formulation is subsequently dispersed by the shearing action of the eyelids that fragments the gel, and the resulting gel fragments are then removed from the ocular surface through the nasolacrimal duct.<sup>33</sup> It is considered that such dynamics of gels on ocular surface induces transient changes in ocular HOAs.<sup>24,34</sup> On the other hand, as eye ointment is not fragmented by blinks as gels, it is slowly cleared from the interpalpebral space through the lacrimal drainage system or by moving onto the lid skin.<sup>1</sup> Furthermore, its high viscosity retards these clearances. This prolonged retention on ocular surface appears to be the main reason why the influence of eye ointment on HOAs was much larger and longer than that of gel-forming solution.

So far, many cases of intraocular ointments after ophthalmic surgeries such as radial keratotomy and phacoemulsification have been reported, and several reports have described severe complications associated with intraocular ointments.<sup>4,35–38</sup> Furthermore, the benefit of immediate postoperative conjunctival antibiotic ointment for the prophylaxis of endophthalmitis has not been proven.<sup>37</sup> Given these aspects of eye ointments and our findings regarding the influence on optical quality, surgeons should use them only when reasonable alternative drops are unavailable.

It should be noted that HOAs and FI returned to the baseline levels after prominent increases at 5 min, but fluctuated for several hours and slightly increased again around 6 h after application of eye ointment. Takaoka *et al*<sup>39</sup> examined the dynamics of an ophthalmic ointment on the ocular surface using a fluorophotometer and a tear lipid layer interference camera (DR-1, Kowa, Nagoya, Japan) during 1 h after administration, and found that the

ointment remained on the ocular surface for at least 1 h. Greaves *et al*<sup>16</sup> investigated the precorneal residence of an ophthalmic ointment using the technique of gamma scintigraphy and revealed that the mean half-time of corneal residence was 108 min. In their study, approximately 30% of the ointment remained on the corneal surface at the end of a 3-h study period.<sup>16</sup> Judging from previous studies and ours, eye ointments remain on the ocular surface for at least several hours after administration, and can significantly affect ocular HOAs even if the amount of residual ointment is relatively small. We at present have no clear explanation for the observed fluctuation and reincrease during 6 h in our study. However, ointment at least in part spreads onto the adjacent skin and also attaches to eyelashes after the bulk application in the conjunctival sac,<sup>1</sup> distributing unevenly on the eyelid margin. The ointment adherent especially to the upper eyelid gradually melts and moves onto the ocular surface, and can mix with tears and deteriorate the regularity and stability of tear film. Moreover, these phenomena are complicatedly modified by blinks. As the subjects were instructed not to wipe their eyelid margins during the study, there is a possibility that the ointment stuck to eyelashes and eyelid skin immediately after the administration occasionally merged into the tear with blinks, and this resulted in the fluctuation and reincrease of HOAs during 6 h in the present study. Further, it is quite different between eyes how the ointment adheres to eyelashes and eyelid skin, melts, and moves into the tear. In fact, the current data of each HOA component showed a large standard deviation at all time points after application of the eye ointment. Such individual variations may also contribute to the present results that the time course of changes in HOAs somewhat fluctuated and did not exhibit a constant decrease after the peak increase.

Unfortunately, we did not examine visual function in this study. However, in another study, we examined contrast sensitivity function after instillation of timolol gel-forming solution, which is the same drug used in this study, and found that the gel-forming solution significantly decreased contrast sensitivity for at least 5 min following instillation, whereas standard timolol solution (without gels) did not reduce contrast sensitivity.<sup>34</sup> On the basis of this finding, it seems quite probable that eye ointment decreases contrast sensitivity during 6 h after application because HOAs and FI at 6 h after administration of eye ointment were still higher than those at 5 min after the gel-forming solution in the present study. The verification of such a long visual deterioration requires further studies.

There are several limitations in this study. First, we examined only one ointment, which is composed of

white petrolatum, lipid paraffin, and purified lanolin. There are many kinds of eye ointments containing various ingredients. Composition of vehicles is also different between ointments. Thus, the present results do not apply to all eye ointments. Ofloxacin eye ointment contains not only lipophilic nonpolar lipid but also hydrophilic polar lipid, which is a key to form a uniform layer on water.<sup>40</sup> Therefore, this ointment is considered to be able to reduce the influence on visual blur after application and has been used in the treatment of dry eyes especially with lipid tear deficiency.<sup>11</sup> However, a lot of ointments available in Japan include only a nonpolar lipid base, which seems to cause a stronger impact on optical quality of the eye. Second, environmental situations such as temperature and humidity may considerably affect the study results. However, we examined only in a limited condition (around 23 °C and 52%). Third, the applied volume of eye ointment was constant. It is interesting to know how HOAs change according to the volume. Further studies with various kinds of eye ointments and different volumes in a variety of conditions are needed to understand the exact influence of eye ointments on the optical quality of the eye in more detail.

In conclusion, sequential analysis of wavefront aberration after administration of eye ointment yields the information that has not been previously obtained by means of conventional methods. We quantitatively demonstrated that the optical influence of the eye ointment on HOAs was larger than that of the gel-forming solution, and the influence lasted for at least several hours. This may be a direct cause of the blurred vision complaints commonly encountered in patients treated with eye ointments. On the basis of the present results, patients should be appropriately informed about the possible reduction in optical quality of the eye, especially when the daily use is unavoidable. In addition, driving or any other procedures requiring high quality of vision are not recommended for several hours after the administration. Although eye ointment is an excellent modality in light of prolonging the drug effect, the influence on optical quality is quite large. Hence, it is hoped that alternative drug delivery system with good bioavailability and less visual impact will be developed.

## Summary

### What was known before

- It is well known that eye ointments cause transient visual blurring after administration.

### What this study adds

- Administration of eye ointment significantly degrades optical quality of the eye by increasing and oscillating higher-order aberrations.

## Conflict of interest

The authors declare no conflict of interest.

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