Ophthalmol Ther (2021) 10:891–904
https://doi.org/10.1007/s40123-021-00368-9

ORIGINAL RESEARCH

Effects of Rebamipide on Differences in Power and Axis of Corneal Astigmatism Between Two Intra-patient Keratometric Measurements in Dry Eyes

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Received: January 30, 2021 / Accepted: June 23, 2021 / Published online: July 22, 2021

ABSTRACT

Introduction: This study investigated the effect of rebamipide on discrepancies in the power and axis of astigmatism between two intra-patient keratometric measurements in patients with dry eyes.

Methods: Fifty-eight dry eyes (with a short tear breakup time [TBUT] of less than 5 s) were analyzed. Patients with dry eye were treated with 2% rebamipide ophthalmic suspension (group R) or Mytear® artificial tear ophthalmic solution (group M) for 4 weeks. TBUT and corneal higher-order aberrations (HOAs) were evaluated at baseline and 4 weeks after treatment. Astigmatism power and axis were measured twice during both evaluations, at 5-min intervals. Baseline and post-treatment measurements were compared. Changes in TBUT and HOAs, and intra-patient discrepancies in astigmatism power and axis measurements were evaluated.

Results: HOAs showed significant positive correlations with intra-patient differences in astigmatism power and axis ($P < 0.001$). At the 4-week post-treatment follow-up, TBUT increased, and HOAs and astigmatism power and axis discrepancies decreased in a significant number of patients in group R ($P < 0.001$). In group M, only differences in astigmatism power decreased in a significant number of cases ($P = 0.005$). The degree of change in the intra-patient difference in astigmatism power between the two post-treatment keratometric measurements was significantly greater in group R than in group M ($P < 0.001$). In group R, baseline HOAs exhibited a significant positive correlation with changes in HOAs and intra-patient differences in astigmatism power (both $P < 0.001$). In group M, baseline HOAs were only significantly correlated with changes in intra-patient differences in astigmatism power ($P = 0.030$).

Conclusion: In dry eyes with short TBUTs, rebamipide significantly improved the corneal surface condition and significantly reduced intra-patient discrepancies in astigmatism power and axis measurements. Rebamipide may improve the accuracy of intraocular lens (IOL) power calculations in dry eyes, particularly when toric IOLs are implanted.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40123-021-00368-9.

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PLAIN LANGUAGE SUMMARY

This study investigated the effect of rebamipide on discrepancies in power and axis of astigmatism between two intra-patient keratometric measurements in patients with dry eyes. Short tear break-up time and corneal high-order aberrations were evaluated at baseline and 4 weeks after treatment. Astigmatism power and axis were measured twice at both evaluations. Baseline and post-treatment measurements were compared, and changes in short tear break-up time and high-order aberrations, as well as intra-patient discrepancies in astigmatism power and axis measurements, were evaluated. High-order aberrations at baseline showed significant positive correlations with intra-patient differences in astigmatism power and axis. Rebamipide significantly improved the corneal surface condition and significantly reduced intra-patient discrepancies in astigmatism power and axis measurements. Rebamipide may improve the accuracy of intraocular lens power calculations in dry eyes, particularly when toric intraocular lenses are implanted.

Keywords: Astigmatism axis; Astigmatic power; Dry eye; Keratometric measurement; Rebamipide

Key Summary Points

Why carry out this study?

Dry eye affects the accuracy of keratometric measurements in patients with dry eye, which may detrimentally affect the accuracy of prediction of postoperative refraction of cataract operation.

No study has previously reported the effect of rebamipide on the accuracy of keratometric measurements.

We investigated whether dry eye treatment with rebamipide would improve the accuracy of keratometric measurements.

What were the study outcomes/conclusions?

Treatment of dry eyes with rebamipide was significantly more effective in improving the accuracy of keratometric measurement than artificial tears.

Further studies should investigate whether preoperative treatment with rebamipide can reduce postoperative refractive error in cases undergoing toric intraocular lens implantation.

INTRODUCTION

In recent years, patient expectations regarding the outcome of cataract surgery have increased [1–4]. Regardless of the type of intraocular lens (IOL) implanted, only removing the cataract and improving blurred vision no longer satisfies patients; accuracy in postoperative refraction is also expected [1]. Gibbons et al. [5] reported that the most common cause of patient dissatisfaction after IOL implantation was blurred vision (68%), which was most often due to postoperative refractive error (57%).

The power of an IOL is calculated using biometric variables, such as corneal curvature, axial length, and anterior chamber depth. Among these variables, corneal curvature is the most influential refractive factor in optical systems; therefore, its accurate measurement is crucial for minimizing postoperative refractive error. Additionally, the advent of toric IOLs allows eye specialists to reduce postoperative corneal astigmatism and improve postoperative refractive error more effectively. After cataract removal, astigmatism derived from the lens is eliminated, and that derived from the cornea can be corrected by implantation of a toric IOL. In a study of 23,239 eyes, Hoffmann and Hütz [6] reported a mean corneal astigmatism of 0.98 ± 0.78 D; corneal astigmatism was less

than 1.00 D in approximately two-thirds of the studied eyes and it was at least 1.00 D in 8.0% of the cases. Thus, a significant number of patients can benefit from correction of corneal astigmatism by the use of toric IOLs.

Accurate preoperative measurement of corneal astigmatism (power and axis) using keratometry is crucial for planning toric IOL implantation. However, keratometry is not always accurate, particularly in cases with irregular astigmatism in the cornea [7]. The most common cause of preoperative irregular astigmatism is dry eye [7, 8]. Thus, dry eye can induce irregular corneal astigmatism, which in turn may affect the accuracy of keratometric measurements, i.e., measurements of corneal astigmatism.

In terms of the relationship between irregular astigmatism, dry eye, and the inaccuracy of measurements of corneal astigmatism, Matossian [9] insisted that an unstable tear film in patients with dry eye produces irregular astigmatism, which causes an overestimation of astigmatism. After dry eye treatment, the ocular surface should be smoother, and the patient will therefore have less astigmatism [9]. Another study also reported that the instability of the tear film induced by dry eye causes irregular astigmatism and that irregular astigmatism is one of the main causes of intra-patient discrepancies in the measurements of astigmatism power and axis [8]. Consequently, 30% of patients require additional keratometric measurements to improve the accuracy of astigmatism measurements [8].

Thus, dry eye may be an influential factor in the accurate measurement of corneal astigmatism using keratometry. Large epidemiological studies have revealed that 5–35% of the population have dry eye [10]. Dry eye can be categorized into two types: aqueous tear-deficient and tear-evaporative types [11]. In Japan, dry eye is diagnosed by a decrease in tear breakup time (TBUT) and by the presence of dry eye symptoms, such as discomfort and visual disturbance [12]. The influence of dry eye on the ocular surface has gained attention in recent years, and studies have reported on the deterioration of ocular surface condition caused by tear film instability [13, 14].

It has been reported that rebamipide (Otsuka Pharmaceutical Co., Ltd., Tokyo, Japan) increases the amount of mucin-like substances and suppresses inflammatory cytokines, which improves the tear film stability and ocular surface condition [13]. Consequently, irregular astigmatism associated with dry eye is also improved after rebamipide administration [13].

Additionally, in a previous study, a significant increase in a mucin-like glycoprotein and *MUC1* and *MUC4* gene expression was found after human corneal epithelial cells were incubated with rebamipide. These data demonstrate that an increase in mucin production induced by rebamipide can cause improvement of keratoconjunctival epithelium damage [15].

We hypothesized that if dry eye treatment with rebamipide could improve irregular corneal astigmatism before toric IOL implantation, it could also lead to a decrease in the differences between intra-patient keratometric measurements, thereby reducing postoperative refractive error. Thus, this study investigated the effect of using rebamipide ophthalmic suspension on differences in intra-patient keratometric measurements (two separate measurements in our case), obtained with an IOLMaster 700 (Carl Zeiss Meditec AG, Jena, Germany), as well as the condition of the cornea in patients with dry eye. To our knowledge, no previous studies have compared the effect of dry eye treatment using rebamipide ophthalmic suspension and an artificial tear solution on the difference in the power and axis of corneal astigmatism over multiple intra-patient keratometric measurements. The findings of this study may result in the development of methods that can significantly improve the accuracy of IOL power calculations in patients with dry eye, particularly when toric IOLs are used.

METHODS

The ethical committees of the Yokosuka Chuo Eye Clinic and Tsurumi Chuo Eye Clinic approved this study. The study adhered to the tenets of the Declaration of Helsinki throughout the data collection process. After a detailed

Table 1 Subject characteristics and baseline data

	Group M (*N* = 28)	**Group R (*N* = 30)**	***p* value**
Age	66.07 (± 12.36)	66.57 (± 12.36)	> 0.05
	[44–86]	[43–86]	
Eye			
Right	15 (53.57%)	15 (50.00%)	> 0.05
Left	13 (46.43%)	15 (50.00%)	
Sex			
Female	20 (71.43%)	23 (76.67%)	> 0.05
Male	8 (28.57%)	7 (23.33%)	
Before treatment			
TBUT	2.61 (± 1.07)	2.73 (± 1.26)	> 0.05
	[1–5]	[1–5]	
HOA difference	0 (± 0.01)	0 (± 0.01)	> 0.05
	[− 0.01 to 0.02]	[− 0.02 to 0.01]	
HOA average	0.31 (± 0.05)	0.31 (± 0.06)	> 0.05
	[0.185–0.385]	[0.18–0.385]	
Power difference	0.27 (± 0.14)	0.3 (± 0.14)	> 0.05
	[0.09–0.54]	[0.05–0.48]	
Axis difference	12.43 (± 6.37)	16.93 (± 8.19)	< 0.05
	[5–27]	[4–33]	
Power average	− 1.24 (± 0.91)	− 1.25 (± 0.86)	> 0.05
	[− 3.07 to − 0.27]	[− 3.15 to − 0.28]	
After treatment			
TBUT	2.75 (± 1.11)	4.4 (± 1.25)	< 0.05
	[1–5]	[2–6]	
HOA difference	0 (± 0.01)	0 (± 0.01)	> 0.05
	[− 0.01 to 0.03]	[− 0.02 to 0.01]	
HOA average	0.3 (± 0.05)	0.26 (± 0.03)	< 0.05
	[0.185–0.39]	[0.185–0.325]	
Power difference	0.24 (± 0.13)	0.13 (± 0.06)	< 0.05
	[0.06–0.54]	[0.03–0.23]	
Axis difference	12.14 (± 6.05)	8.73 (± 5.04)	< 0.05
	[3–22]	[2–19]	

Table 1 continued

	Group M ($N = 28$)	Group R ($N = 30$)	p value
Power average	− 1.23 (± 0.91)	− 1.18 (± 0.85)	> 0.05
	[− 3.005 to − 0.3]	[− 3.28 to − 0.265]	
Difference B − A			
TBUT difference B − A	0.14 (± 0.52)	1.67 (± 0.76)	< 0.05
	[− 1 to 2]	[0–3]	
HOAs difference B − A	− 0.01 (± 0.01)	0.05 (± 0.03)	< 0.05
	[− 0.06–0.01]	[0.005–0.115]	
Power difference B − A	0.04 (± 0.05)	0.17 (± 0.1)	< 0.05
	[0–0.21]	[0.01–0.35]	
Axis difference B − A	1.5 (± 1.4)	8.27 (± 6.29)	< 0.05
	[0–5]	[0–22]	

The difference in power and axis indicates the intra-patient differences in power and axis measurements
TBUT tear breakup time, *HOAs* high-order aberrations

explanation of the possible results, informed consent was obtained from all subjects.

Patients

We included the eyes of patients with dry eye who were scheduled to undergo cataract surgery. Patients were included if they had dry eye as diagnosed on the basis of the Japanese dry eye diagnostic criteria (TBUT ≤ 5 s and presence of dry eye symptoms, such as eye discomfort and visual disturbance) [12]. Individuals with the following medical history were excluded from this study: ocular trauma, nasolacrimal drainage apparatus abnormality, permanent occlusion of the lacrimal puncta or temporary punctal plug occlusion, meibomian gland dysfunction, and use of contact lenses.

The subjects with dry eye were randomly assigned, using permuted block randomization, to receive 4 weeks' treatment with either 2% rebamipide ophthalmic suspension (group R) or Mytear® ophthalmic solution (group M). Subject characteristics and baseline data are presented in Table 1.

Dry Eye Treatment

The subjects were asked to cease using all other eye drops and to use only 2% rebamipide ophthalmic suspension (Mucosta ophthalmic suspension UD2%; Otsuka Pharmaceutical Co.) in group R or artificial tear Mytear® ophthalmic solution (Mytear®; Senju Pharmaceutical Co., Ltd., Osaka, Japan) in group M, four times daily, for 4 weeks. Mytear® contains sodium chloride (5.5 mg), potassium chloride (1.6 mg), dried sodium carbonate (0.6 mg), dibasic sodium phosphate hydrate (1.8 mg), and boric acid (12 mg), in a 1 mL solution. The viscosity of Mytear® is 2.22 mm^2/s (at 20 °C ± 0.1 °C).

Examination of Tear Function, Ocular Surface, and Corneal Astigmatism

TBUT was measured three times using a wettable fluorescein strip, and the average of the three consecutive TBUTs was calculated. The corneal higher-order aberrations (HOAs) within a 4-mm-diameter area centered on the cornea were evaluated using a CASIA 2 (Tomey

Corporation, Nagoya, Japan). To investigate the difference in the power and axis of corneal astigmatism in multiple intra-patient measurements according to the eye drops used, we performed two separate measurements of astigmatism power and axis using the IOLMaster 700 (Carl Zeiss Meditec AG), at a 5-min interval. These repeated measurements were collected at baseline and after 4 weeks of dry eye treatment in both group R and group M.

Statistical Analysis

We used the Bell Curve for Excel version 1.03 (Social Survey Research Information Co., Ltd., Tokyo, Japan) to analyze all statistical data. We conducted a post hoc power analysis to determine the power of our analysis with the given sample size (n = 58). Before dry eye treatment, the correlation between the difference in corneal astigmatism power and axis in the repeated intra-patient measurements, and the HOAs in both groups were analyzed using Spearman's rank correlation test. Thereafter, we compared the number of subjects who showed a change between pre and post dry eye treatment in TBUT and HOAs, and the difference in corneal astigmatism power and axis in the repeated measurements, by means of the Wilcoxon signed-rank test. Next, the degree of change in TBUT and HOAs between pre and post dry eye treatment were measured and compared in group R and group M. In addition, the degree of changes between pre and post dry eye treatment in the difference in power and axis of astigmatism between the repeated intra-patient measurements were compared between group R and group M and were analyzed by means of the Mann–Whitney U test. The correlations between HOAs before dry eye treatment and the degree of change in the variables were also analyzed using Spearman's rank correlation test.

In order to investigate the differences among the patients in before and after treatment groups, we used the Friedman rank-sum test, in which the patients were considered as the block group.

Statistical significance was set at $P < 0.05$ (two-sided P values).

RESULTS

Fifty-eight eyes of 58 subjects (15 men and 43 women) were diagnosed with dry eyes. Thirty patients received dry eye treatment with rebamipide (group R) and 28 patients withMytear®

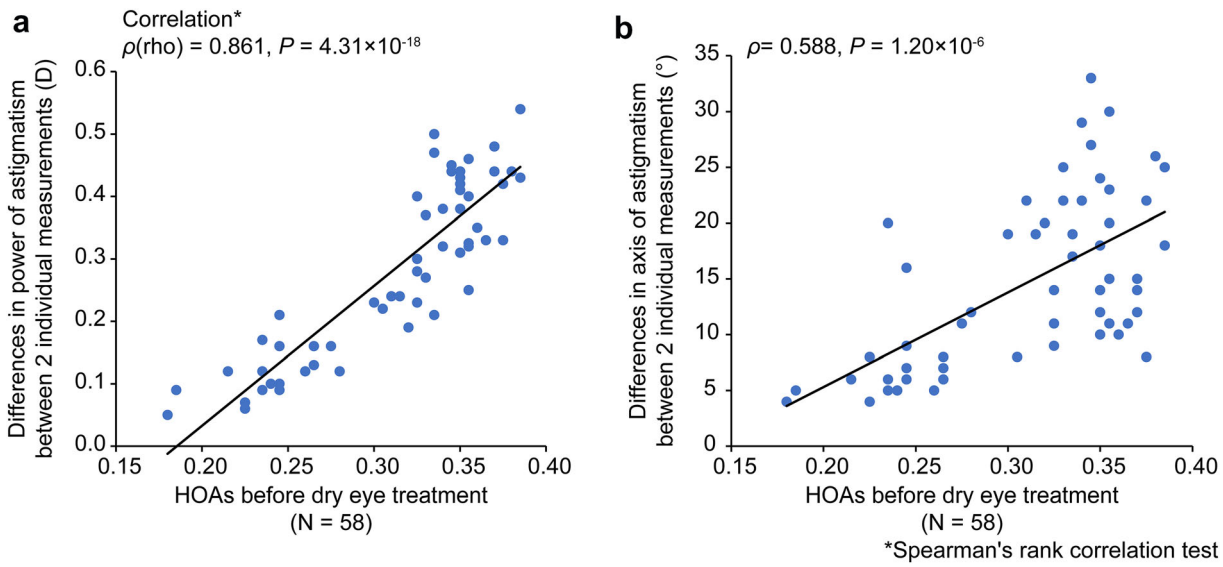

Fig. 1 Correlation between HOAs and the differences in intra-patient astigmatism **a** power and **b** axis measurements before dry eye treatment. HOAs higher-order aberrations

Table 2 The number of cases that showed differences in variables before and after dry eye treatment

	TBUT (*n*)	HOAs (*n*)	Power of astigmatism* (*n*)	Axis of astigmatism* (*n*)
Group R ($n = 30$)				
Difference** = 0	1	0	0	1
Difference** < 0	29	3	1	1
Difference** > 0	0	27	29	28
P value (Wilcoxon signed-rank test)	2.56×10^{-6}	3.69×10^{-6}	2.35×10^{-6}	3.34×10^{-6}
Group M ($n = 28$)				
Difference** = 0	23	3	4	7
Difference** < 0	4	7	7	10
Difference** > 0	1	18	17	11
P value (Wilcoxon signed-rank test)	0.178	0.054	0.005	0.543

Wilcoxon signed-rank test: comparison of the number of cases that showed differences in the four variables, before and after dry eye treatment

Group R 2% rebamipide ophthalmic suspension, *Group M* Mytear® ophthalmic solution, *TBUT* tear breakup time, *HOAs* higher-order aberrations; *n* = cases

**Difference indicates the absolute difference in the variables before and after dry eye treatment

(group M). The age of subjects ranged from 43 to 86 years (mean 66.5 ± 12.2 years) in group R, and from 43 to 86 years (mean 66.1 ± 12.1 years) in group M.

Treatment adherence was assessed by nurses on scheduled dates, using the treatment regimen instructions. The nurses ensured that all subjects followed and completed the regimen. Throughout the study period, no adverse effects occurred as a result of the eye drops.

The post hoc power analysis showed that our analysis with the given sample size ($n = 58$) has a very good power to detect medium ($d = 0.5$) effect sizes. More specifically, it showed that for the Wilcoxon signed-rank test, the power is 96.3%.

Before dry eye treatment, the differences in the power (Fig. 1a) and axis (Fig. 1b) of corneal astigmatism between the two intra-patient measurements was significantly and positively correlated with HOAs (rho [ρ] = 0.861 and $\rho = 0.588$, respectively) ($P < 0.001$).

The exact numbers of subjects who showed differences before and after dry eye treatment in TBUT and HOAs, as well as the differences in the power and axis of corneal astigmatism between the two intra-patient measurements, are presented in Table 2. After dry eye treatment, TBUT increased in a significant number of patients in group R ($P < 0.001$) but not in group M ($P = 0.178$) (Table 2). The degree of increase in TBUT before and after dry eye treatment in group R was significantly higher than that in group M ($P < 0.001$) (Table 3).

After dry eye treatment, HOAs decreased in a significant number of patients in group R ($P < 0.001$) (Table 2) but not in group M ($P = 0.054$) (Table 2). The degree of decrease in HOAs before and after dry eye treatment in group R was significantly larger than that in group M ($P < 0.001$) (Table 3). Regarding the difference in astigmatism power between the two intra-patient repeated measurements, first, after the dry eye treatment, the difference in astigmatism power decreased in a significant

Table 3 Comparison of change in TBUT, HOAs, and difference in power and axis of astigmatism between two intra-patient measurements at each visit in group R and group M before and after dry eye treatment

	Pre-treatment	Post-treatment	*P**
TBUT (s)			
Group R	2.73 ± 1.24	4.40 ± 1.23	1.58×10^{-9}
Group M	2.61 ± 1.05	2.75 ± 1.09	
HOAs (μm)			
Group R	0.31 ± 0.06	0.26 ± 0.03	1.48×10^{-6}
Group M	0.31 ± 0.05	0.30 ± 0.05	
Difference in power of astigmatism between two intra-patient measurements at each visit			
Group R	0.30 ± 0.14	0.13 ± 0.06	9.82×10^{-7}
Group M	0.27 ± 0.14	0.24 ± 0.13	
Difference in axis of astigmatism between two intra-patient measurements at each visit			
Group R	16.93 ± 8.05	8.73 ± 4.96	1.46×10^{-7}
Group M	12.43 ± 6.25	12.14 ± 5.94	

Results are expressed as means ± standard deviation
Group R 2% rebamipide ophthalmic suspension, *Group M* MyTear® ophthalmic solution, *TBUT* tear breakup time
*Mann–Whitney *U* test: comparison of the degree of change in TBUT, HOAs, and difference in power and axis of astigmatism between two intra-patient measurements at each visit before and after dry eye treatment between group R and group M

number of patients in group R ($P < 0.001$) and group M ($P = 0.005$) (Table 2). Second, the degree of change before and after dry eye treatment in group R was significantly larger than that in group M ($P < 0.001$) (Table 3). In terms of the difference in astigmatism axis between the two intra-patient repeated measurements, after dry eye treatment, the axis measurement decreased in a significant number of patients in group R ($P < 0.001$) (Table 2) but not in group M ($P = 0.543$) (Table 2). Moreover, the degree of change in group R was significantly larger than that in group M ($P < 0.001$) (Table 3). In vector analysis, the difference in astigmatism between the two intra-patient repeated measurements at each visit significantly decreased after dry eye treatment in group R ($P < 0.001$), but not in group M ($P = 0.274$). Additionally, the degree of the decrease in group R was significantly larger than group M ($P < 0.001$) (Table 4).

In group R, HOAs before dry eye treatment showed significant correlations with two other parameters: first, with the degree of change in HOAs from before to after the dry eye treatment ($\rho = -0.853$, $P < 0.001$) (Fig. 2a); and second, with the degree of change in the difference in astigmatism power between the two intra-patient measurements ($\rho = 0.761$, $P < 0.001$) (Fig. 2a). In group M, HOAs before dry eye treatment showed a significant positive correlation only with the degree of change in the difference in astigmatism power between the two intra-patient measurements ($\rho = 0.411$, $P = 0.030$) (Fig. 2b). The significance of this correlation in group M was much lower than that in group R.

The analysis with the Friedman rank-sum test revealed the following (Table 5): the "HOA difference" was not significantly different ($P > 0.05$) between the before and after treatment groups among the patients. Moreover, the "TBUT" showed a statistically significant difference ($P < 0.01$) between the before and after treatment groups among the patients. Additionally, both the "power difference" and the "axis difference" were significantly different ($P < 0.01$) between the before and after treatment groups.

DISCUSSION

To the best of our knowledge, no previous study has reported the effect of rebamipide ophthalmic suspension on keratometric measurements calculated using the IOLMaster (Carl Zeiss Meditec AG) in dry eyes with short TBUTs.

Table 4 Comparison of changes in the difference in astigmatism between two intra-patient measurements at each visit in group R and group M, before and after dry eye treatment, in vector analysis of astigmatism

	Pre-treatment	Post-treatment	*P**	*P***
Group R	0.54 ± 0.37	0.28 ± 0.23	1.73×10^{-6}	3.96×10^{-6}
Group M	0.40 ± 0.26	0.38 ± 0.27	0.274	

*Wilcoxon signed-rank test: comparison of the difference in the astigmatism between two intra-patient measurements in group R and group M before and after dry eye treatment

**Mann–Whitney *U* test: comparison of the degree of change in difference in the power of astigmatism between two intra-patient measurements before and after dry eye treatment between group R and group M

Consistent with the findings of previous studies [16, 17], this study demonstrated that dry eye caused deterioration of the ocular surface condition and that the larger the HOAs before dry eye treatment, the larger was the difference in the astigmatism power and axis between two intra-patient repeated measurements. Regarding the effect of dry eye treatment on ocular surface conditions, we showed that treatment with rebamipide, but not with the Mytear® ophthalmic solution, improved TBUT and HOAs. Moreover, the difference in astigmatism power between the two intra-patient measurements was decreased after dry eye treatment in a significant number of subjects in both group R and group M. However, the degree of decrease was significantly greater in group R than in group M. Moreover, only group R included a significant number of subjects with a decrease in the difference between the two repeated intra-patient astigmatism axis measurements. Furthermore, the larger the HOA before dry eye treatment, the larger was the decrease of the difference in astigmatism power between two

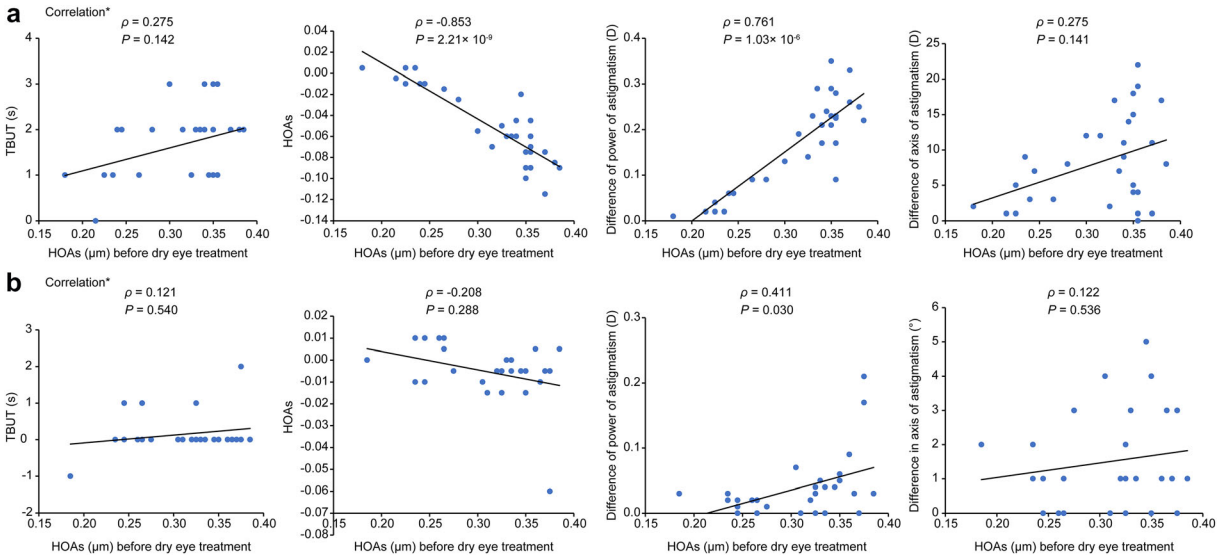

Fig. 2 Correlation between pre-treatment HOAs and differences in variables pre and post treatment in **a** group R and **b** group M. All variables in the vertical axis indicate the degree of change between pre- and post-treatment (post dry eye treatment − pre dry eye treatment). The difference in astigmatism power and axis represents the degree of change in discrepancies in intra-patient astigmatism power and axis measurements (absolute values) from pre- to post-treatment. *Spearman's rank correlation test. Reba 2% rebamipide ophthalmic suspension, HOAs higher-order aberrations, ATs artificial tears

Table 5 Friedman rank sum test results

	Friedman chi-squared	*P* value
HOA difference	1.0889	0.297
HOA average	22.273	2.37×10^{-6}
TBUT	30.118	4.07×10^{-8}
Power difference	27.769	1.37×10^{-7}
Power average	2.5714	0.109
Axis difference	15.68	7.50×10^{-5}

HOA higher-order aberration, *TBUT* tear breakup time

intra-patient repeated measurements after dry eye treatment in both group R and group M. However, this correlation was more significant in group R.

Astigmatism management has become increasingly crucial as the demand for multifocal IOLs has increased [18, 19]. Hayashi et al. [18] reported that astigmatism greater than 1.0 D needs to be corrected to ensure better visual acuity in patients with bifocal IOLs. Diffractive trifocal IOLs provide good distance and near vision with better intermediate vision than bifocal IOLs, and this is the main reason for the rapid increase in their popularity [20–22]. However, it has recently been reported that distance vision in trifocal IOLs is more vulnerable to residual astigmatism than bifocal IOLs and that astigmatism correction is needed when it exceeds 0.75 D [23]. Thus, minimizing postoperative residual astigmatism has become more important with the success of cataract surgery, as the intricacy of optical multifocal IOL design is increasing. Therefore, it is essential to measure corneal astigmatism accurately and to choose the power and axis of toric IOLs correctly to achieve successful outcomes [24].

Keratometric measurement of healthy corneas is highly reproducible, regardless of whether conventional or advanced keratometry is used [25]. However, Holladay [8] reported that, because of discrepancies in astigmatism power and axis in intra-patient keratometric measurements, about 30% of patients require additional keratometric measurements to obtain greater accuracy, particularly when toric IOLs are used. Irregular astigmatism is one of the main causes of discrepancies in astigmatism power and axis in intra-patient keratometric measurements. Irregular astigmatism can be quantified by HOAs, and its most common cause is dry eye [8]. Montés-Micó et al. [26] demonstrated that patients with dry eye have larger HOAs than those with non-dry eye and that the increase in HOAs in dry eyes is mainly caused by an increase in tear film instability. Koh et al. [16] stated that tear film instability causes the tear film to break up rapidly and thicken irregularly. In terms of the influence of corneal irregularity on the accuracy of astigmatism measurements obtained with the IOLMaster (Carl Zeiss Meditec AG), Roh et al. [27] reported that astigmatism assessment as measured with this device was less accurate in patients with marked HOAs.

In the present study, rebamipide was effective in reducing the differences in intra-patient measurements in patients with dry eyes. A previous study reported that HOAs measured in patients with dry eyes and superficial punctate keratopathy (SPK) in the central cornea are higher than those measured in patients with dry eyes without SPK in the central cornea [28]. In the present study, dry eye was diagnosed on the basis of the Japanese dry eye diagnostic criteria [29], i.e., a short TBUT and the presence of dry eye symptoms, regardless of ocular surface damage and tear deficiency. Therefore, the wide range of HOAs demonstrated in our study may be explained by the possible inclusion of patients both with and without SPK in the central cornea.

In clinical settings, artificial tears may be administered to patients with dry eye immediately before keratometric measurement, particularly when the difference in astigmatism power and axis between intra-patient repeated measurements is large. The intention behind this is to make the surface of the cornea smoother and to stabilize the tear film. However, Röggla et al. [30] demonstrated that instilling artificial tears prior to keratometry measurements significantly affected the astigmatism power, particularly in dry eyes. They suggested that keratometric measurements should be performed more than 5 min after

artificial tear administration and insisted that the higher the viscosity of the eye drops, the greater and longer their influence. Thus, artificial tear administration prior to keratometric measurements may not be an appropriate option for improving accuracy. We consider that ocular surface management prior to examination may be a better option for improving the accuracy of keratometric measurements.

In our study, we compared the effect of rebamipide and Mytear® ophthalmic solution on improving the condition of the ocular surface and the differences in astigmatism power and axis between two intra-patient keratometric measurements. Rebamipide reduced HOAs in patients with dry eye and notable pre-treatment HOAs. This result was supported by those of Koh et al. [16], who showed that rebamipide decreases HOAs, resulting in improved ocular surface conditions. The present study also indicated that larger pre-treatment HOAs showed marked reduction after treatment with rebamipide, but not after treatment with Mytear®. This result was also supported by Inoue et al. [17, 31], who reported that artificial tears do not significantly reduce HOAs in patients with dry eye. Thus, in terms of the effect of rebamipide and Mytear® on the improvement of the ocular surface condition, our results supported previous studies in many respects.

While some previous studies have reported negative effects of irregular astigmatism on the accuracy of keratometric measurements [8, 26, 32], we are unaware of any previous studies that have dealt with the effect of dry eye treatment with rebamipide on the difference in astigmatism power and axis between two intra-patient measurements. As mentioned above, one previous study highlighted the problem of differences in intra-patient keratometric measurements [8]. Therefore, our study focused on the effect of dry eye treatment with rebamipide tears on the differences in the power and axis between two intra-patient repeated measurements. In this study, in a significant number of cases, treatment with rebamipide significantly decreased HOAs and intra-patient differences in astigmatism power and axis measurements. These results are plausible, given that rebamipide improves tear stability, resulting in irregular astigmatism in dry eyes [16]. In a significant number of cases, treatment with Mytear® reduced the differences in astigmatism power. This result was unexpected because treatment with artificial tears in previous studies had not decreased irregular astigmatism [17, 31]. However, the degree of reduction in the differences was significantly greater in the rebamipide group than in the Mytear® group, as predicted. Therefore, rebamipide was significantly more effective than Mytear® in improving the accuracy of keratometric measurements. Furthermore, the present study showed that, in the rebamipide group, the baseline HOAs were significantly positively correlated with the degree of change between baseline and post dry eye treatment, and the differences in astigmatism power between the two intra-patient measurements. These results support the concept that the larger the baseline HOA, the stronger is the indication for rebamipide treatment before performing keratometric measurements. To the best of our knowledge, there have been no previous reports that have investigated the correlations between HOAs at baseline, the degree of change in HOAs, and the differences in astigmatism power and axis between intra-patient repeated measurements after dry eye treatment with rebamipide. As mentioned above, Koh et al. [28] reported that dry eyes with SPK in the central cornea show more HOAs than dry eyes without SPK in the central cornea. It has been reported that rebamipide positively affects the corneal epithelial layer by improving structural irregularities and increasing the growth of corneal epithelial cells [15, 33]. One possible cause of more HOAs at baseline in the current study could be SPK in the central corneas, which could be improved by rebamipide. Clearly, future research should investigate SPK in the central cornea, to clarify the relationship between HOAs, differences in intra-patient astigmatism power and axis measurements, and the effect of rebamipide.

One of the limitations of our study was the small sample size. Another limitation is that we applied the Japanese definition of dry eye, which differs from other scientific

classifications, such as the Adelphi and DEWS definitions. Therefore, in further research, the investigation should be performed using other dry eye definitions to evaluate whether different definitions could affect the results of the study. The absence of objective assessment of the cornea in terms of SPK and corneal staining is also a limitation since it can be a useful assessment of the astigmatism power and higher-order aberration. Additionally, the effects of changes in HOAs and the degree of the difference in astigmatism power and axis on postoperative refraction were not investigated. Therefore, since many factors are involved in IOL calculation, the improvement of accuracy of keratometry power is not sufficient to claim improved IOL calculation. Furthermore, it would be interesting to compare the effects of different types of tear film stabilizing ophthalmic solutions on keratometric measurements.

CONCLUSIONS

Dry eye treatment with rebamipide significantly improved the condition of the ocular surface and reduced the differences in astigmatism power and axis in two intra-patient repeated measurements obtained using the IOLMaster 700. In future, improvements in the postoperative refractive error involving dry eye cases treated with rebamipide following toric IOL implantation should be investigated to scrutinize the relationship between the accuracy of postoperative refraction and the improvement of accuracy of keratometric power.

ACKNOWLEDGEMENTS

Funding. No funding or sponsorship was received for this study or publication of this article. The authors funded the journal's rapid service fee.

Author Contributions. TT, AM, and NM made substantial contributions to the conception and design, data acquisition, or data analysis and interpretation. TT and AM drafted the article and critically revised it for important intellectual content.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical Writing, Editorial, and Other Assistance. We would like to thank Editage (https://www.editage.com) for English language editing.

Disclosures. Takeshi Teshigawara, Akira Meguro, Nobuhisa Mizuki have nothing to disclose.

Compliance with Ethics Guidelines. The study was approved by the ethics committee of the Yokosuka Chuo Eye Clinic. The ethics committee of the Yokosuka Chuo Eye Clinic did not issue an approval reference number. The study was performed in accordance with the Helsinki Declaration of 1964, and its later amendments. Informed consent was obtained from all patients.

Data availability. The data supporting the results reported in the manuscript are available from the corresponding author.

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