ORIGINAL RESEARCH

The Effect of Diquafosol Ophthalmic Solution on Clinical Parameters and Visual Function in Soft Contact Lens-Related Dry Eye

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ABSTRACT

Introduction: This study evaluated the efficacy and safety of diquafosol ophthalmic solution (DQS) in soft contact lens (SCL)-related dry eye using artificial tear as a control.

Methods: This study enrolled 26 patients with SCL-related dry eye. DQS and artificial tears (AT) were instilled into the right and left eyes, respectively, with their SCLs on. Dry eye examinations (including tear film breakup time, tear volume, and staining score) were performed and visual function (including contrast sensitivity) was also evaluated before (at baseline) and after treatment (at 4- and 8-week examinations). Subjective symptoms were assessed separately in each eye using a questionnaire on dry eye in contact lens wearers. The results were compared before and after treatment, and between the right eyes treated with DQS (the DQS eye) and the left eyes treated with AT (the AT eye) using the mixed effect model.

Results: Corneal and conjunctival staining scores at 8-week examination were significantly lower than those at baseline in the DQS eye ($p = 0.03$; $p < 0.001$, respectively), but no significant changes were observed in the AT eye. Most subjective symptoms improved significantly in both the DQS and AT eyes. However, major subjective symptoms (dryness and blurry vision) improved significantly only in the DQS eye at 8-week examination. Contrast sensitivity at 8-week examination in the DQS eye improved significantly at 12 cycles/degree compared to baseline ($p = 0.001$) and was significantly better than that in the AT eye ($p = 0.03$). There were no adverse events related to DQS or AT.

Conclusions: DQS was effective and safe for SCL-related dry eye. DQS also improved contrast sensitivity.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR), Identification No. UMIN000024064.

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Key Summary Points

Why carry out this study?

Contact lens wearing is thought to be one of the main causes of dry eye development and deterioration.

Diquafosol ophthalmic solution is a P2Y$_2$ receptor agonist approved for the treatment of dry eye that promotes water and mucin secretion from conjunctiva.

The purpose of this study was to evaluate the efficacy and safety of diquafosol ophthalmic solution in soft contact lens-related dry eye, comparing with artificial tears as a control.

What was learned from the study?

This study confirmed that diquafosol ophthalmic solution improved corneal and conjunctival staining scores, subjective symptoms and contrast sensitivity, and the safety was also acceptable.

Diquafosol is a useful option for soft contact lens-related dry eye.

INTRODUCTION

Dry eye is a multifactorial disease characterized by unstable tear film causing a variety of symptoms and/or visual impairment, potentially accompanied by ocular surface damage [1]. It is known to be highly influenced by the patient's lifestyle [2] and living environment [3]. In particular, contact lens (CL) wearing is thought to be one of the main causes of dry eye development and deterioration [4], and CL wearers exhibit significantly more ocular symptoms than non-wearers [5, 6].

CL divides the tear film into two layers, the upper side (pre) and the lower side (post) of the lens [7, 8], disrupting the tear film lipid layer [9] and reducing the tear film thickness [10]. In such conditions, the tear film easily evaporates and breaks up, resulting in the development of dry eye [11–13]. The breakup of the tear film on the CL surface degrades the optical uniformity of the ocular surface and causes the loss of visual function, such as contrast sensitivity deterioration [14]. In addition, the reduction in tear volume on the CL surface leads to increased friction between the CL and corneal surface [9]. Thus, dry eye treatment for CL wearers is focused on the hydration of the eye surface with artificial tears (AT) [15, 16]. However, the treatment for hydration is a major challenge for such patients because of the frequent need for instillation of ophthalmic solutions. Besides, the soft contact lens (SCL) has to be removed during instillation to avoid the possibility of the absorption of the preservative agents, such as benzalkonium chloride (BAK) contained in the ophthalmic solutions, into the SCLs; this is also toxic to the ocular surface [17].

As recently reported, diquafosol, a P2Y$_2$ receptor agonist, is effective against dry eye by promoting the secretion of water and mucin from the conjunctival epithelium [18, 19], leading to the prolongation of the tear film breakup time (BUT), amelioration of the corneal and conjunctival epithelial damage, and improvement of the subjective symptoms [20–26]. The ability of diquafosol to stimulate mucin as well as water secretion is effective in increasing tear volume and improving wettability on the surface of the eyes [22, 26]. Thus, the instillation of diquafosol relieved subjective symptoms when wearing CLs [24, 25]. In addition, it should be emphasized that the current formulation of diquafosol ophthalmic solution (DQS; Diquas ophthalmic solution 3%, Santen Pharmaceutical, Osaka, Japan) in multi-dose (MD) bottle packaging has changed the preservative from BAK to chlorhexidine gluconate solution in Japan and Asia countries. This BAK-free MD bottle of DQS can be instilled in the eyes wearing SCL. Several studies have examined the efficacy of DQS including BAK on CL-related dry eye [24, 25]. However, the efficacy

and safety of BAK-free DQS on SCL-related dry eye, which can be instilled more safely, have not been evaluated. In addition, the influence of DQS on the quality of vision (QOV) is still unknown. Contrast sensitivity, which is defined as the ability to detect differences in luminance between adjacent areas, is a fundamental feature of vision, and this measurement can provide useful information on visual function, which may not be obtained by standard visual acuity testing. Several studies have shown that contrast sensitivity function significantly correlates with some abilities associated with the quality of life, such as reading speed [27, 28], mobility and walking speed [29], driving performance [30], and computer task accuracy [31]. Hence, it is extremely important to assess contrast sensitivity in the eyes with optical instability of the ocular surface, such as with dry eye and contact lens wearing.

This study investigated the efficacy, including contrast sensitivity assessment and safety of DQS instillation in SCL-related dry eye, using AT as a control.

METHODS

Study Design

This study was an open-label study prospectively conducted at two hospitals (Ibaraki Seinan Medical Center Hospital and Namegata District Medical Center) in Ibaraki prefecture, Japan. All participants were provided with a full explanation about the study and they provided written informed consent. This study was registered with the University Hospital Medical Information Network Clinical Trials Registry (UMIN-CTR) (http://www.umin.ac.jp/, Identification No. UMIN000024064).

Compliance with Ethics Guidelines

This study followed the tenets of the Declaration of Helsinki, and was approved by the institutional review board and the ethics committee at each study site (namely the Ibaraki Seinan Medical Center Hospital ethics committee and Namegata District Medical Center ethics committee, reference number; 16-2).

Subjects

The inclusion criteria for this study were aged at least 16 years, routinely wearing SCLs in both eyes (at least 6 h per day and 5 days per week), positive subjective symptoms (at least one symptom with a frequency score of 1 or more), tear film abnormalities (BUT of 5 s or less, or Schirmer test of 5 mm or less), and total staining scores (corneal score + conjunctival score) of 6 or more. Only wearers of the daily disposable or biweekly replacement SCLs were included in this study. Cosmetic tinted SCLs were not allowed. SCL materials and focus types were not restricted, but patients were required to use the same brand of SCL in their left and right eyes. The exclusion criteria for this study were that subjects had received any dry eye treatment within 14 days prior to the start date of this study, or continued to use other topical ophthalmic solutions that can affect the study results. Subjects with ocular infection or other ocular diseases besides dry eye and refractive errors were also excluded from this study. The information such as subject background, age, gender, type of SCL, and SCL wearing time were collected. Information on systemic administration was not collected.

Visual Function Examination

The subjects underwent visual acuity and contrast sensitivity testings under photopic conditions. Corrected distance visual acuity was measured using standard high-contrast visual acuity charts. Contrast sensitivity was measured for each eye separately with CSV-1000 (Vector Vision Co, Greenville, OH, USA), and the area under the log contrast sensitivity function (AULCSF) was calculated in accordance with a previously described method [32].

SCL Fitting Test

SCL fitting including stable position, rotation, movement of the lens, and uplifting of the lens edge was checked for each eye with a slit-lamp microscope. If it was deemed inappropriate, the SCL was replaced with an appropriate one.

Dry Eye Examinations

Tear volume was measured by meniscometry strips with SCL on the eye [33]. After an interval of at least 5 min after SCLs were removed from both eyes, and 2 μL of preservative-free 1% sodium fluorescein solution was administered into the lower conjunctival sac with a micropipette. Subsequently, BUT was measured for up to 10 s, and repeated three times for each eye. The mean value was calculated and used for subsequent analyses. After that, the corneal staining score was determined. Similarly, 2 μL of preservative-free 1% lissamine green solution was then administered into the lower conjunctival sac with the micropipette, and the conjunctival staining score was also determined. These assessments were performed on the basis of the classification of the National Eye Institute [34]. In brief, the corneal staining score was evaluated in five areas and the conjunctival in six areas, with each area scored on a 0- to 3-point scale (from 0, no damage to 3, damage over the entire area). After an interval of at least 5 min after those staining examinations, Schirmer I test was performed only at baseline under unanesthetized conditions using sterilized Tear Production Measuring Strips (Ayumi, Tokyo).

Questionnaire

Subjective symptoms while wearing SCLs were assessed separately in each eye using a questionnaire. The questionnaire consists of questions on the frequency and the intensity of 14 symptoms, namely dryness, eye fatigue, blurry vision, foreign body sensation, discomfort, itching, closing eyes for relief, redness, photophobia, tearing, crusty eyelid, grittiness, soreness, and burning. These 14 symptoms were selected with reference to the reported "contact lens dry eye questionnaire" [35, 36]. The frequency was scored on a 0 to 4 scale from 0 (never), 1 (occasionally), 2 (sometimes), 3 (frequently), to 4 (always) while the intensity was from 1 (slightly), 2 (weak), 3 (moderate), 4 (strong), to 5 (very strong). The frequency and intensity scores for each symptom were multiplied for each eye, and the product was used for the analyses.

Dry eye was diagnosed in this study based on positive subjective symptoms (at least one symptom with a frequency score of 1 or more), tear film abnormalities (BUT of 5 s or less, or Schirmer I test 5 mm or less), and total staining scores (corneal score + conjunctival score) of 6 or more.

Instillation of Ophthalmic Solutions

Subjects who met the inclusion criteria for dry eye diagnosis in both eyes were prescribed DQS and preservative-free AT (Soft Santear, Santen Pharmaceutical, Osaka, Japan) for the treatment of SCL-related dry eye. The active ingredient of DQS was 3% diquafosol sodium with additives including KCl, NaCl, chlorhexidine gluconate, sodium hydrogen phosphate, disodium edetate hydrate, and a pH conditioner. The active ingredients of AT were 0.1% KCl and 0.4% NaCl without BAK. These eye drops are widely available in Japan. Subjects were required to instill DQS into the right eye and AT into the left eye, six times daily for 4 weeks with their SCLs on, and to remove their SCLs before sleeping (after completing the sixth instillation). At the 4-week visit, subjects who were able to extend the study participation were asked to continue the instillations until the 8-week visit. All examinations were performed before treatment (at baseline) with DQS or AT and after the treatment (at 4- and 8–week examination). At 4- and 8-week visits, all examinations were performed at least 1 h after instillation of DQS and AT. At the 4- and 8-week visits, the subjects were asked about the instillation adherence rate during the period since the last visit, using the following four criteria: Instilled completely (100%), mostly

(75–99%), sometimes (25–74%), and hardly (below 25%).

Adverse Events

At every visit, ocular health was checked by detailed slit-lamp microscopy. In addition, the occurrence of systemic adverse events was also checked throughout the study period. If adverse events were found, the findings were reported.

Statistical Analysis

Results of the baseline examinations were analyzed using the paired t test. Comparisons before and after treatment, between the left and right eyes were performed using the mixed effect model. All statistical analyses were performed by Bio statistical research (Tokyo, Japan) using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA); p values less than 0.05 were considered significant.

RESULTS

Study Subjects

Table 1 shows the demographic data. Twenty-eight subjects fulfilled the inclusion and exclusion criteria, and were enrolled in this study. After the baseline examinations, DQS and AT were instilled into the right and left eyes, respectively. Among these, 26 subjects (2 men, 24 women, 37.6 ± 9.6 years old) completed the 4-week examination, and 19 subjects completed the 8-week examination. There were 14 daily disposable SCL wearers and 12 biweekly replacement SCL wearers. Eleven subjects wore silicone hydrogel SCLs and 15 wore non-silicone hydrogel SCLs. The average SCL wearing time was 14.4 ± 2.2 h per day. Table 2 shows the results of the baseline examinations such as the visual function and dry eye assessments. There were no significant differences in subject background between DQS and AT, with the exception of the mean value of 18 cycles per degree (cpd) of contrast sensitivity. Regarding the instillation adherence rate, at the 4-week

Table 1 Demographic data

Demographic data	n (%)
Number of subjects analyzed	26
Sex	
Male	2 (7.7)
Female	24 (92.3)
Age (years)	
Mean ± SD	37.6 ± 9.6
Median	37.5
Min/max	22/61
Type of SCL	
Daily disposable SCL	14 (53.8)
Biweekly replacement SCL	12 (46.2)
Wearing time of SCL (h/day)	
Mean ± SD	14.4 ± 2.2
Median	15.0
Min/max	10/18

SCL soft contact lens, *SD* standard deviation

visit, 11.5% (3 cases) instilled completely, 84.6% (22 cases) mostly, and 3.8% (1 case) sometimes. At the 8-week visit, 15.8% (3 cases) instilled completely, 73.7% (14 cases) mostly, and 10.5% (2 cases) sometimes. There was no subject who instilled the ophthalmic solutions hardly. There was no difference in adherence between the left and right eyes throughout the period.

Dry Eye Examination

Table 3 shows the results of the dry eye examination before and after treatment. Corneal staining scores at the 8-week examination were significantly lower than those at baseline in the right eyes treated with DQS (the DQS eye) ($p = 0.03$), but no significant changes were observed in the left eyes treated with AT (the AT eye). Similarly, conjunctival staining scores at 4- and 8-week examinations significantly

Table 2 Results of baseline examinations in the DQS eye and the AT eye

Examinations	DQS (26 eyes)	AT (26 eyes)	*p* value
Visual acuity (logMAR)	− 0.06 ± 0.03	− 0.06 ± 0.04	0.91
Contrast sensitivity at four spatial frequencies (log contrast sensitivity)			
3 cpd	1.6 ± 0.2	1.6 ± 0.2	0.20
6 cpd	1.9 ± 0.1	1.8 ± 0.2	0.46
12 cpd	1.5 ± 0.2	1.6 ± 0.2	0.22
18 cpd	1.1 ± 0.3	1.2 ± 0.3	0.02*
AULCSF	1.3 ± 0.1	1.3 ± 0.1	0.65
Corneal staining score	1.8 ± 1.7	1.8 ± 1.4	1.00
Conjunctival staining score	8.0 ± 2.7	8.2 ± 3.1	0.60
Tear film breakup time (s)	2.4 ± 2.0	2.3 ± 1.5	0.66
Tear volume (mm)	2.1 ± 1.3	1.9 ± 1.1	0.37
Schirmer I test (mm)	13.6 ± 11.7	15.4 ± 11.2	0.25

Figures are expressed as mean ± standard deviation
DQS the right eyes treated with diquafosol ophthalmic solution, *AT* the left eyes treated with artificial tears, *logMAR* logarithm of the minimal angle resolution, *cpd* cycles per degree, *AULCSF* area under the log contrast sensitivity function
*Statistically significant by paired *t* test ($p < 0.05$)

decreased in the DQS eye ($p < 0.001$), but no significant changes were found in the AT eye. When compared between the DQS eye and the AT eye, conjunctival staining scores in the DQS eye were significantly lower than those in the AT eye at 4-week examination ($p = 0.02$). BUT and tear volume at 8-week examination increased from those at baseline in the DQS eye, but not significantly.

Dry Eye-Related Symptoms

Figure 1 shows the changes in 14 subjective symptoms before and after the treatment. Most subjective symptoms significantly improved in both the DQS eye and the AT eye. There was no significant difference in the subjective symptoms between the DQS eye and the AT eye. However, dryness and blurry vision, which were major subjective symptoms of dry eye, significantly improved only in the DQS eye at 8-week examination compared with those at baseline ($p = < 0.002$, $p = 0.004$ respectively).

Visual Function Examination

There were no significant changes in the visual acuity before and after treatment in either eye (Table 3). Figure 2 shows the changes in contrast sensitivity at four spatial frequencies before and after treatment. Contrast sensitivity significantly improved after treatment compared to the baseline value at high spatial frequencies, such as at 12 cpd ($p = 0.001$, at 8-week examination) and 18 cpd ($p = 0.04$, at 4-week examination), in the DQS eye; but no significant changes were observed in the AT eye. When compared between the DQS eye and the AT eye, contrast sensitivity at 12 cpd was significantly better in the DQS eye than in the AT eye at 8-week examination ($p = 0.03$). Figure 3 shows the changes in AULCSF before and after treatment. AULCSF significantly increased in the DQS eye at both 4-week ($p = 0.01$) and 8-week examinations ($p < 0.001$), and in the AT eye only at 8-week examination ($p = 0.03$). When compared between the DQS eye and the AT eye, there was no significant difference in AULCSF.

Table 3 Results of visual acuity and dry eye examinations before and after treatment

Examinations	Visit	DQS			AT			p value between DQS and AT
		n (eye)	Estimate (95% CI)	p value vs. baseline	n (eye)	Estimate (95% CI)	p value vs. baseline	
Visual acuity (logMAR)	Baseline	26	− 0.06 (− 0.08, − 0.05)	–	26	− 0.06 (− 0.08, − 0.05)	–	–
	4-week	26	− 0.07 (− 0.08, − 0.05)	0.86	26	− 0.06 (− 0.07, − 0.04)	0.27	0.36
	8-week	19	− 0.06 (− 0.08, − 0.04)	0.70	19	− 0.06 (− 0.08, − 0.04)	0.56	0.89
Corneal staining score (score)	Baseline	26	1.77 (1.21, 2.33)	–	26	1.77 (1.21, 2.33)	–	–
	4-week	26	1.31 (0.75, 1.86)	0.16	26	1.88 (1.33, 2.44)	0.72	0.21
	8-week	19	0.98 (0.34, 1.62)	0.03*	19	1.58 (0.95, 2.22)	0.61	0.24
Conjunctival staining score (score)	Baseline	26	7.96 (6.86, 9.06)	–	26	8.19 (7.09, 9.29)	–	–
	4-week	26	6.12 (5.01, 7.22)	< 0.001***	26	8.08 (6.98, 9.18)	0.83	0.02*
	8-week	19	5.96 (4.74, 7.17)	< 0.001***	19	7.49 (6.27, 8.71)	0.23	0.12
Tear film breakup time (s)	Baseline	26	2.40 (1.61, 3.19)	–	26	2.27 (1.48, 3.06)	–	–
	4-week	26	2.90 (2.11, 3.69)	0.24	26	2.04 (1.25, 2.83)	0.59	0.23
	8-week	19	3.16 (2.27, 4.05)	0.11	19	2.64 (1.75, 3.53)	0.43	0.56

Table 3 continued

Examinations	Visit	DQS			AT			p value between DQS and AT
		n (eye)	Estimate (95% CI)	p value vs. baseline	n (eye)	Estimate (95% CI)	p value vs. baseline	
Tear volume (mm)	Baseline	26	2.12 (1.54, 2.69)	–	26	1.88 (1.31, 2.46)	–	–
	4-week	26	2.12 (1.54, 2.69)	1.00	26	1.46 (0.88, 2.04)	0.22	0.38
	8-week	19	2.34 (1.68, 3.01)	0.55	19	1.73 (1.07, 2.39)	0.69	0.48

DQS the right eyes treated with diquafosol ophthalmic solution, *AT* the left eyes treated with artificial tears, *logMAR* logarithm of the minimal angle resolution, *CI* confidence interval

$^{*}p < 0.05$, $^{***}p < 0.001$ by mixed effect model

Safety

Two adverse events were observed during the study. One was a pollen allergy, and the other was nasal sinusitis. They were not causally related to DQS and AT. Both adverse events occurred prior to the 4-week visit. These two cases dropped out of the study because they had to discontinue SCL wearing or take systemic administration of antibiotics for 10 days. No other adverse events were observed during the study period.

DISCUSSION

This study investigated the effect of BAK-free DQS instillation on SCL-related dry eye. As a result, this study confirmed its favorable efficacy and acceptable safety. DQS instillation significantly reduced corneal and conjunctival staining scores, but AT did not. In addition, DQS instillation generally improved subjective symptoms, especially major symptoms such as dryness and blurry vision. Furthermore, DQS instillation significantly increased contrast sensitivity. Although some improvements in subjective symptoms and contrast sensitivity were achieved after instillation of AT, overall improvements were remarkable after instillation of DQS. The first reason that DQS was effective in SCL-related dry eye was the good instillation adherence rate throughout the study period. There is a vicious cycle between the epithelium and the aqueous humor layer in dry eye [37], and it considered important to continue eye drop therapy with good adherence to stop this vicious cycle. Secondly, the mechanism of action of DQS, which is effective against dry eye, may be suitable for the treatment of SCL-related dry eye. DQS promotes the secretion of water and mucin from the conjunctival epithelium [18, 19], retaining and stabilizing the tear fluid. And, administration of DQS to SCL wearers with dryness symptoms increased biomarkers of membrane-associated mucin [24] and improves epithelial wettability [37]. It thought that CL causes SCL-related dry eye dividing the tear film into two layers, the upper side (pre) and the lower side (post) of the lens [7, 8], disrupting the tear film lipid layer [9] and reducing the tear film thickness [10]. DQS instillation has also been reported to significantly increase tear meniscus height in healthy subjects wearing SCL for up to 60 min [38] and to accumulate both pre- and post-CL tear fluid in rabbit eyes [39]. Tear volume in this study increased in DQS eyes before and after treatment, although not significantly, whereas it did not increase in AT eyes (Table 3). Similarly, BUT was also prolonged in DQS eyes, although not significantly, and was more prolonged than in
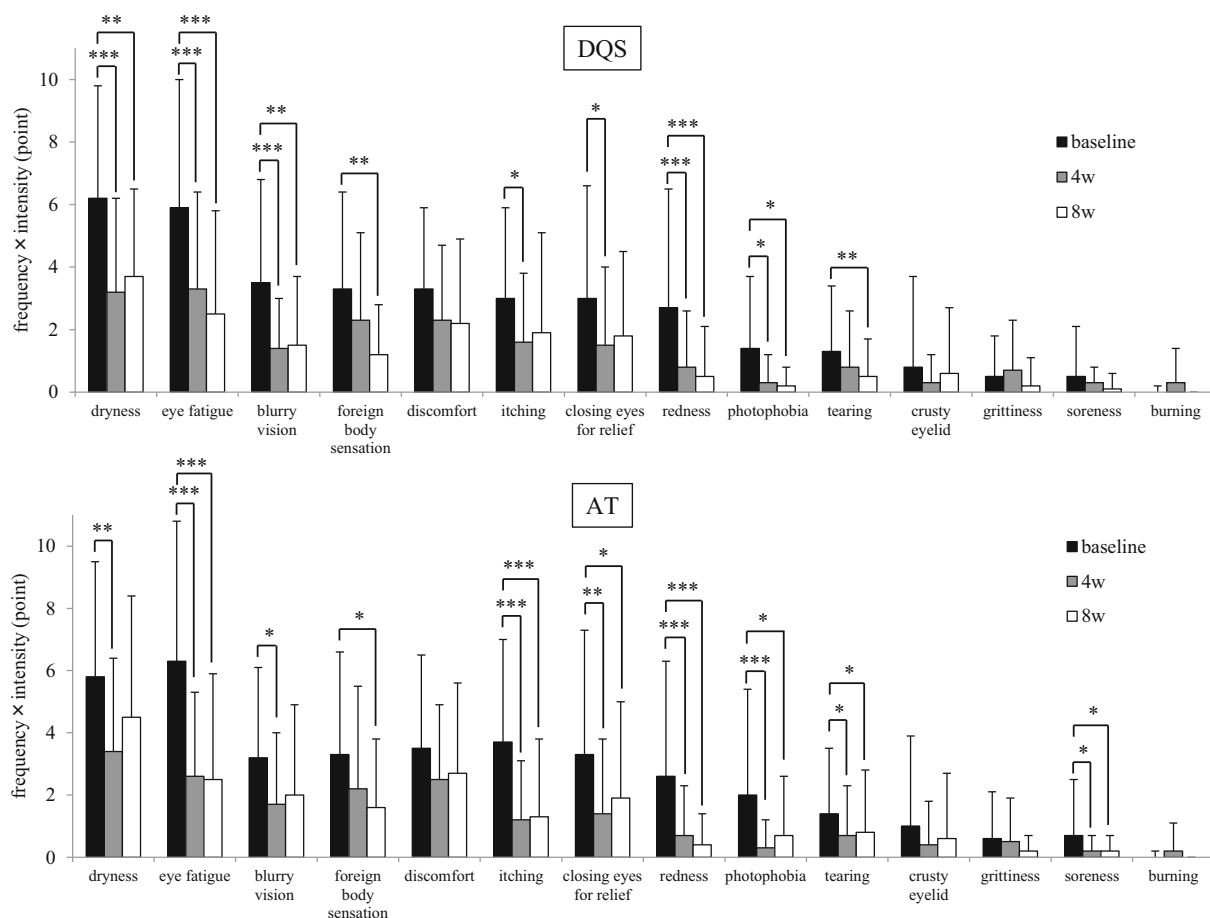
Fig. 1 Changes in 14 subjective symptoms before and after treatment. Data are expressed as mean value and standard deviation. DQS the right eyes treated with diquafosol ophthalmic solution, AT the left eyes treated with artificial tears, 4w after instillation for 4 weeks, 8w after instillation for 8 weeks. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ by mixed effect model

AT eyes (Table 3). These results seem to support the pharmacological effects of DQS. The improvement in epithelial damage in this study may be due to the increase in the tear volume of the lower side of SCL by DQS, which reduced friction between the SCL and the epithelium and decreased contact between the SCL and the ocular surface. It is also emphasized that no adverse events related to DQS were observed throughout the study period.

Some previous studies reported the efficacy of DQS in SCL-related dry eye [24, 25], showing that DQS instillation significantly improved BUT, corneal and conjunctival staining scores, and subjective symptoms. The results were very similar to the findings of this study in terms of the improvements in corneal and conjunctival staining scores and subjective symptoms. However, the previous studies merely evaluated the drug efficacy compared to the pre-treatment conditions, and did not set up a control drug. In contrast, AT was employed as a control drug in this study, and this comparative setting proved the predominance of DQS for the treatment of SCL-related dry eye. This is the first study to show the superiority of DQS over a positive control.

This study included contrast sensitivity testing as a QOV evaluation. The tear film is unstable in patients with dry eye, which considerably affects the optical quality of the eye [40]. Koh et al. reported significant increases in
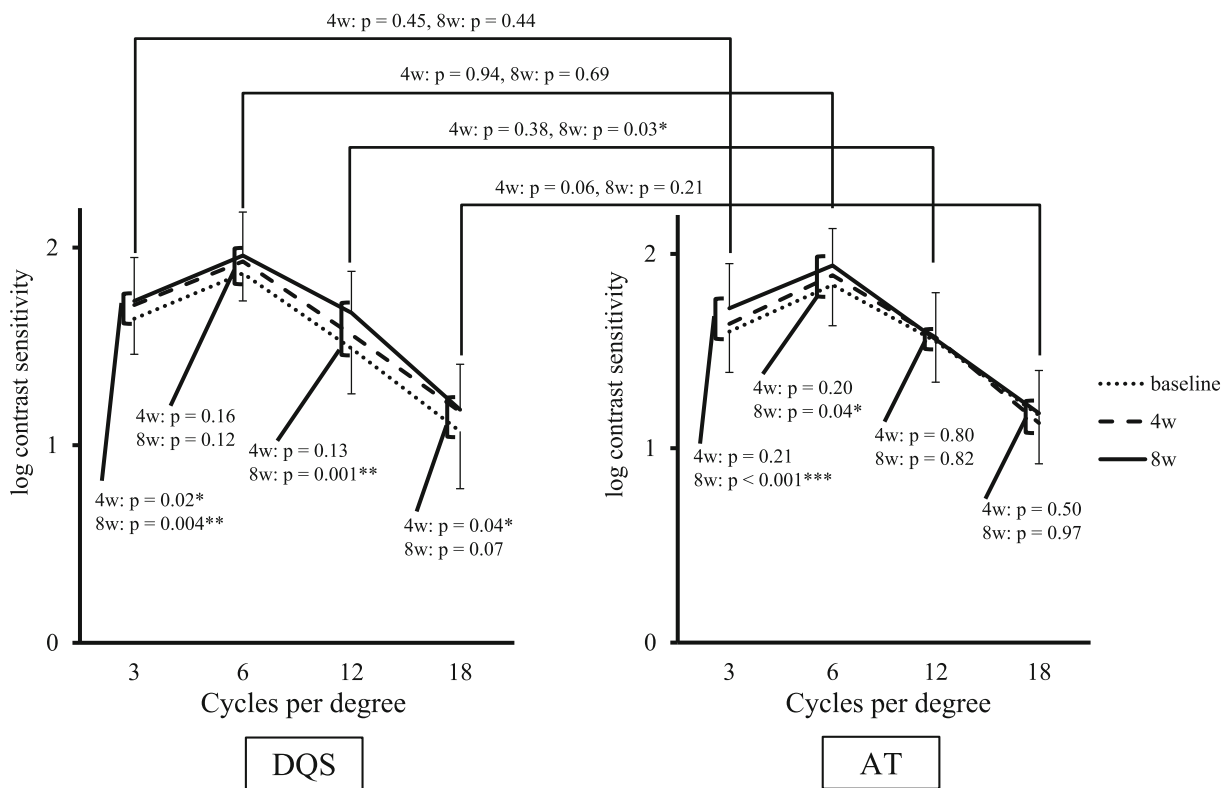
Fig. 2 Changes in contrast sensitivity at four spatial frequencies before and after treatment. Data are expressed as mean value and standard deviation. DQS the right eyes treated with diquafosol ophthalmic solution, AT the left eyes treated with artificial tears, 4w after instillation for 4 weeks, 8w after instillation for 8 weeks. $^*p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$ by mixed effect model
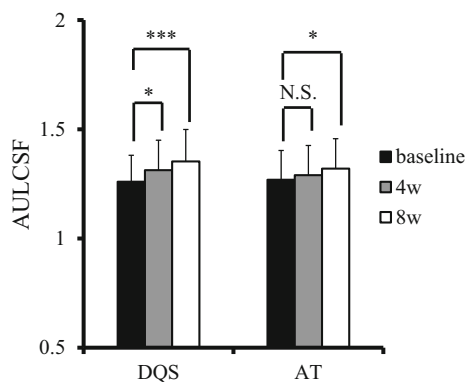

Fig. 3 Changes in AULCSF. Data are expressed as mean value and standard deviation. DQS the right eyes treated with diquafosol ophthalmic solution, AT the left eyes treated with artificial tears, 4w after instillation for 4 weeks, 8w after instillation for 8 weeks, AULCSF the area under the log contrast sensitivity function, N.S. not significant. $^*p < 0.05$, $^{***}p < 0.001$ by mixed effect model

ocular higher-order aberrations in patients with dry eye [40]. The same research group also clarified that long-term use of DQS significantly reduced ocular higher-order aberrations in patients with dry eye [41]. However, the effect of DQS on contrast sensitivity has not been investigated so far. This study revealed for the first time that treatment with DQS for more than 4 weeks significantly improved contrast sensitivity function; and the improvement was better than that of AT, especially at higher spatial frequencies such as 12 and 18 cpd. It has been reported that contrast sensitivity significantly decreases from middle to high spatial frequencies when pre-CL tear film dried and broke up [14]. Once again, DQS stimulates not only water but also mucin secretion [18, 19], increased biomarkers of membrane-associated mucin [24], and improved epithelial wettability [37]. It has been reported that DQS accumulated

both pre- and post-CL tear fluid [39]. Thus, it is considered that the use of DQS recovered the stability of pre- and post-SCL tear film, improved SCL fitting, and eventually improved contrast sensitivity in this study. As high spatial frequencies of contrast sensitivity closely influence reading capabilities and finer resolution tasks [42], it is very likely that DQS improves such tasks. Further studies should be conducted to confirm these effects of DQS by assessing the reading speed.

Another novel finding in this study is the considerable improvement of the corneal and conjunctival staining scores after instillation of DQS. Koh et al. elucidated that dry eyes with superficial punctate keratopathy (SPK) in the central corneal region significantly decreased the contrast sensitivity (including AULCSF and letter contrast sensitivity) compared with those without SPK in the central corneal region and normal eyes [43]. In this study, DQS significantly reduced corneal staining score, but AT did not. This may have also contributed to the better improvement of contrast sensitivity after instillation of DQS.

ATs have been applied for a long time to treat SCL-related dry eyes [15, 16], but the effect seems temporary because they supply only the watery component of tear. On the basis of the results of this study, DQS is better suited for the treatment of SCL-related dry eye than artificial tears.

This study has several limitations. First, it is not clear that the subjects suffered from SCL-related dry eye or had fundamental dry eye without SCL since the tear stability and ocular staining assessments were made following SCL wear. Second, the sample size was small, the subjects were not randomized, and the ophthalmic solutions were not masked in this study. These factors may have influenced the study results. Therefore, a well-designed study with a larger sample size and a widely used therapeutic agent as a control such as sodium hyaluronate ophthalmic solution is warranted to confirm the current results. Third, since the SCLs of material, design, the replacement schedules, cleaning, and maintenance options, and so on were not unified in this study, there were many external factors affecting the results

of this study. To eliminate these external factors, another study with a unified SCL should also be conducted.

CONCLUSIONS

DQS improved ocular surface damage, subjective symptoms, and visual performance in patients with SCL-related dry eye. The safety of the DQS was also acceptable.

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Compliance with Ethics Guidelines. All participants were provided with a full explanation about the study and they provided written informed consent. This study followed the tenets of the Declaration of Helsinki, and was approved by the institutional review board and the ethics committee at each study site (namely the Ibaraki Seinan Medical Center Hospital ethics committee and Namegata District Medical Center ethics committee, reference number; 16-2).

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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