ELSEVIER

CLINICAL INVESTIGATIONS

Disposable Eyelid-Warming Device for the Treatment of Meibomian Gland Dysfunction

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Purpose: To assess the clinical efficacy of a newly developed disposable eyelid-warming device (Eye Warmer) for the treatment of meibomian gland dysfunction (MGD).

Methods: The Eye Warmer was applied for 5 minutes to 44 eyes of 22 patients who exhibited decreased tear break-up time (BUT) and dry-eye symptoms. Its efficacy was assessed on the basis of BUT and dry-eye symptoms in the short-term study. In the therapeutic study, the Eye Warmer was applied to 34 eyes of 17 MGD patients with decreased BUT and dry-eye symptoms for 5 minutes once a day for 2 weeks. The 16 eyes of 8 patients served as untreated controls. We examined tear film lipid layer interference patterns, BUT, meibomian gland secretion, and dry-eye symptoms in both groups before and after the treatment.

Results: BUT and dry-eye symptoms significantly improved after the treatment in both the short-term and the therapeutic study ($P < .01$). The incidence of normal tear lipid layer in the treated group was significantly higher after treatment (28 eyes [82.4%]) than before (19 eyes [55.9%]) ($P = .036$). The incidence of meibomian gland obstruction was significantly decreased after treatment (14 eyes [41.2%]) compared to before treatment (26 eyes [76.5%]) ($P = .006$).

Conclusions: Warming the eyelids with the Eye Warmer improved the stability and uniformity of the tear lipid layer in MGD patients by melting the meibomian gland lipid. Our study demonstrates the usefulness of the Eye Warmer for the treatment of MGD. **Jpn J Ophthalmol 2003;47:578–586** © 2003 Japanese Ophthalmological Society

Key Words: Meibomian gland dysfunction, tear film, temperature, warm compress.

Introduction

The meibomian glands secrete lipid into tears, and the lipid forms an oily layer of preocular tear film that reduces tear evaporation.[1] Obstructive-type meibomian gland dysfunction (MGD) is characterized by inspissation of meibomian gland lipid, resulting in hyposecretion of lipid into tears.[2] MGD is reported to be a major cause of ocular surface abnormalities and ocular discomfort.[3]

Some eyelid-related diseases, such as MGD,[4,5] chalazion,[6] and seborrheic blepharitis[7] have been successfully treated with warm compresses. McCulley et al found that different compositions of the ester fraction of meibomian gland secretions can have different melting points and that chronic blepharitis can cause a shift toward lipid with higher melting points, producing a stagnant, less dynamic tear film.[8–10] Warming the eyelids is thought to improve blood flow and cause melting of meibomian gland lipid.[11] We have reported that an infrared eye-warming instrument could safely and predictably increase eyelid temperature.[12] Later, Kao Corporation (Tokyo) developed a disposable eyelid-warming device called ''Eye Warmer'' that contains iron (Fe) and generates heat and water vapor when it is exposed to oxygen (O_2). We conducted a prospective study to assess the clinical efficacy of the Eye Warmer for the treatment of MGD. First, we assessed the short-term efficacy of treatment (5-minute warming, once) and the safety of the Eye Warmer for warming the

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eyelids by measuring the temperature of the eye. We then assessed the therapeutic value of this device when used for 5 minutes of warming once a day for 2 weeks. We also performed the tear function test, evaluated the ocular surface, examined the meibomian glands, and assessed dry-eye symptoms.

Materials and Methods

Disposable Eyelid-Warming Device

The mechanism of heat generation of the Eye Warmer is the oxidation of iron (Fe). The chemical reaction scheme of the heat and water vapor generating mechanism is as follows: $Fe + 3/4\ O_2 + 3/2\ H_2O \rightarrow Fe(OH)_3 + 96$ kcal/mol, where a certain amount of H_2O is initially added to the powder formulation. Once the reaction is initiated, the H_2O is heated and vaporized into the atmosphere. The chemical reaction is automatically terminated in about 20 minutes, after completion of the evaporation of the H_2O. Iron and the other ingredients are formulated, vacuum-packed into oval shapes, and heat-sealed at a sealing strength of more than 106 gf/15 mm, to prevent accidental seal breakdown. Preliminary laboratory research has shown that there will be no toxic effect from the material used, which comes in contact with the patient's skin. The Eye Warmer is an eye-mask type and is attached with a Velcro headband (Figure 1). It should be removed from its sealed package only immediately before use.

Subjects

Short-term efficacy. Twenty-two patients (44 eyes) (5 men and 17 women; age range, 23–71 years; mean ± SD age, 44.9 ± 15.7 years) who exhibited decreased tear break-up time (BUT) (≤5 seconds) in both eyes and dry-eye symptoms were recruited for the study.

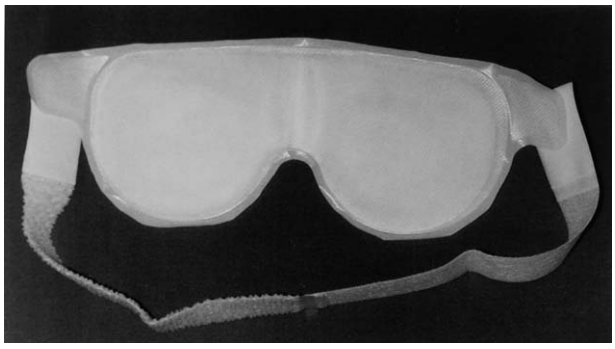

Figure 1. Disposable eyelid-warming device (Eye Warmer). It contains iron (Fe), which generates heat and water vapor when exposed to oxygen (O_2).

Therapeutic efficacy. Seventeen patients (34 eyes) (1 man and 16 women; age range, 26–78 years; mean ± SD age, 53.8 ± 14.7 years) who exhibited decreased BUT (≤5 seconds) in both eyes, MGD, and dry-eye symptoms were recruited for the study. Eight patients (16 eyes) (1 man and 7 women; age range, 26–78 years; mean ± SD age, 53.4 ± 17.5 years, not notably different from the other group) who exhibited decreased BUT (≤5 seconds) in both eyes, MGD, and dry-eye symptoms served as untreated controls.

The patients' symptoms were determined by a questionnaire, as described previously.[13] All patients had at least 3 chronic dry-eye symptoms among 12 typical dry-eye symptoms, including ocular fatigue, foreign-body sensation, redness, ocular pain, and dry sensation. We excluded from the study any patients with eye disorders that could have affected the ocular surface (eg, infectious conjunctivitis, allergic diseases, autoimmune diseases, and collagen diseases) as well as patients who wore contact lenses. Patients whose eyes exhibited excessive meibomian lipid secretion (seborrheic MGD) were also excluded, because seborrheic MGD is a distinct clinical entity.[2] Patients with highly decreased reflex tear production (≤10 mm) by the Schirmer II test (nasal stimulation) were also excluded.[14] Informed consent was obtained from all patients after the nature of the procedures had been fully explained.

Assessment of the Ocular Surface and Meibomian Gland Function

We conducted examinations to obtain background data on the two groups in the therapeutic study. The examinations were conducted in the following order to eliminate the influence of one procedure on another. First, we examined tear film lipid layer interference patterns with a specular reflection video-recording system (DR-1, Kowa, Tokyo). In a masked fashion, an investigator, other than those who collected the interference pattern data, classified the patterns observed into five grades: grade 1, somewhat gray color, uniform distribution; grade 2, somewhat gray color, nonuniform distribution; grade 3, a few colors, nonuniform distribution; grade 4, many colors, nonuniform distribution; and grade 5, corneal surface partially exposed.[15] A previous study showed that only somewhat gray interference with or without stripes (grade 1 and grade 2) was observed in normal eyes.[15] Second, 2 μL of mixtures (1:1) of a preservative-free solution containing 1% fluorescein and 1% rose bengal dissolved in saline was used for the vital staining tests.[16] The results were assessed semiquantitatively by using a grading scale for fluorescein staining in the cornea (range of grades, 0–3) and a scale for rose bengal staining in

Jpn J Ophthalmol
Vol 47: 578–586, 2003

both the cornea and conjunctiva (range of grades, 0–9), according to previously described methods.[13,16,17] Third, BUT was measured three times, and the measurements were averaged. Fourth, we performed the cotton thread test by placing cotton thread dyed with a pH indicator (phenol red) under the lateral portion of the inferior palpebral margin for 15 seconds. The length of the wet portion was measured, and the value was used as an indicator of the amount of tears in the inferior cul-de-sac.[18] Fifth, after application of a topical anesthetic agent (0.4% benoxinate hydrochloride [oxybuprocaine hydrochloride] [Benoxil], Santen, Osaka) to the patient's eye, we performed the Schirmer test for 5 minutes.

Sixth, to evaluate the obstruction of the meibomian glands, transillumination (meibography) was performed by using a transillumination device for vitrectomy with a fiber optic light source (L-3920, Inami, Tokyo) and a 20-gauge disposable fiber optic light guide.[19–25] The lower eyelid of each eye was folded over the fiber optic light guide transilluminating the glands of the lower eyelid. Loss of visible structure of the meibomian glands (gland dropout) was considered evidence of the presence of MGD, because this finding has been reported to be a good parameter for MGD-associated ocular surface changes.[3,26] Of the more than 20 meibomian glands in the lower eyelid, only the central 8 were routinely examined as described previously.[22] The number of dropout glands among the central eight glands was recorded. Finally, to assess obstruction of the meibomian gland orifices, moderate digital pressure was applied to the upper tarsus and the degree of ease in expressing meibomian gland secretion was evaluated semiquantitatively as follows: grade 0, clear secretion easily expressed; grade 1, cloudy secretion expressed with moderate pressure; grade 2, cloudy secretion expressed with more than moderate pressure; and grade 3, no secretion expressed even with intense pressure.[3,27] The procedure was performed by a single investigator (A.M.), who attempted to apply the same pressure throughout the study. Grades 2 and 3 were considered to indicate the obstruction of the meibomian gland orifices. In this study, ''MGD'' is defined as the absence of visible gland structure or the presence of obstruction of meibomian gland orifices.

Measurements

Short-term efficacy. All measurements were performed in a wind-free room at constant temperature (25.5 ± 0.5ºC), humidity (30 ± 6%), and brightness.

To examine the safety and efficacy of the Eye Warmer, we measured eye temperature by noncontact infrared radiation thermography with a Thermal Vision Laird 3 (Nikon, Tokyo). We applied the Eye Warmer 2 minutes after opening the package, as preliminary studies had shown that the Eye Warmer reached its highest temperature (45ºC) in 2 minutes and that the temperature remained above 40ºC for 15 minutes. The Eye Warmer was applied to the closed eyes of 6 subjects for 5 minutes. The temperature of the upper and lower eyelids and cornea of their right eyes was measured immediately before and after warming the eyelids. To assess the safety of the Eye Warmer, we applied it to the open eyes of 3 other subjects for 5 minutes. Corneal temperature was measured immediately before and after this direct exposure to the Eye Warmer. The temperature measurements and analysis were performed as described previously.[12,28]

To assess its short-term efficacy, the Eye Warmer was applied to patients' closed eyes, once, for 5 minutes. Immediately before and after warming the eyelids for 5 minutes, BUT and the most common dry-eye symptoms, that is, ocular fatigue and dry sensation, were assessed on a visual analog scale. We presented a sheet of paper with a 10-cm–long line drawn on it, with ''none'' written at the left end and ''severe'' at the right end, and asked the subject to mark the point on the line that corresponded to the severity of the symptom with an ''X.'' An ''X'' 3 cm from the left end was considered equal to a score of 3. The larger the score, the more severe was the subjective symptom. We then evaluated the relationship between the improvement in BUT (total improvement of BUT in both eyes) and the rates of improvement in symptoms (score [before treatment-after treatment]/score [before treatment] × 100) (%).

Therapeutic efficacy. To assess its therapeutic efficacy, the Eye Warmer was applied to the patients' closed eyes for 5 minutes once a day at a convenient time of their choice for 2 weeks in the treated group, and no eyelid warming was performed in the patients in the untreated control group. The findings most affected by warming the eyelids, that is, the tear film lipid layer interference pattern, BUT, and meibomian gland secretion, were examined before and after the treatment by a masked observer. The examination after the treatment was performed on the day following the last use of the Eye Warmer. The dry-eye symptoms (ocular fatigue and dry sensation) were assessed in the same manner as in the short-term study.

Statistical Analysis

All data are presented as means ± SD. Between-group differences in BUT, cotton thread test, the Schirmer test, gland dropout on meibography, and symptom scores were evaluated by the Student *t*-test. The Mann–Whitney *U*-test was used to evaluate differences in the results of

the fluorescein and rose bengal staining scores. Simple regression analysis was used to compare the improvement in BUT with rates of symptom improvement. The χ^2 test was used to compare the distribution of interference grades, and the Fisher exact probability test was used to compare the distribution of meibomian gland secretion grades. A level of $P < .05$ was accepted as statistically significant.

Results

Short-term Efficacy

Figure 2 shows a typical thermogram of the eyelids before and after warming with the Eye Warmer. Red represents the warmer areas and blue represents the cooler ones, indicating that the eyelid temperature increased after using the Eye Warmer. Temperature increased by 5.6ºC in the upper eyelid and by 6.0ºC in the lower eyelid. The mean temperature of the cornea increased to 37.4ºC with the eyes closed and 37.5ºC with the eyes open, and it never rose above 38.3ºC after 5 minutes of warming (Table 1).

BUT before treatment (2.77 ± 1.03 seconds) was significantly increased after treatment (5.20 ± 2.54 seconds) ($P < .01$, Figure 3), and dry-eye symptoms improved significantly as well ($P < .01$, Figure 3). The mean improvement rates for ocular fatigue and dry sensation were 45.7% ± 30.0% and 52.2% ± 27.9%, respectively. The relationship between the improvement in BUT and rates of improvement in symptoms are shown in Figure 4. There were positive correlations between the improvement in BUT and the rates of improvement in ocular fatigue and dry sensation (correlation coefficient, $r = 0.48, 0.57$, respectively).

Table 1. Temperature After Warming with the Eye Warmer Once for 5 Minutes*

Area	Prewarming (ºC)	Postwarming (ºC)	Change (ºC)
Upper eyelid	34.4 ± 0.3	40.0 ± 0.3	5.6 ± 0.4
Lower eyelid	34.2 ± 0.3	40.3 ± 0.6	6.0 ± 0.8
Cornea (eyes closed)	34.1 ± 0.4	37.4 ± 0.4	3.4 ± 0.4
Cornea (eyes open)	33.7 ± 0.7	37.5 ± 0.7	3.9 ± 1.0

*Data are shown as means ± SD.

Therapeutic efficacy. The basic characteristics of the ocular surface, tear function, and meibomian gland function before treatment in the two groups are summarized in Table 2. There were no significant differences in fluorescein or rose bengal staining, BUT, the cotton thread test, or gland dropout on meibography between the two groups. The results of the Schirmer test in the untreated group were slightly higher than in the treated group ($P = .04$).

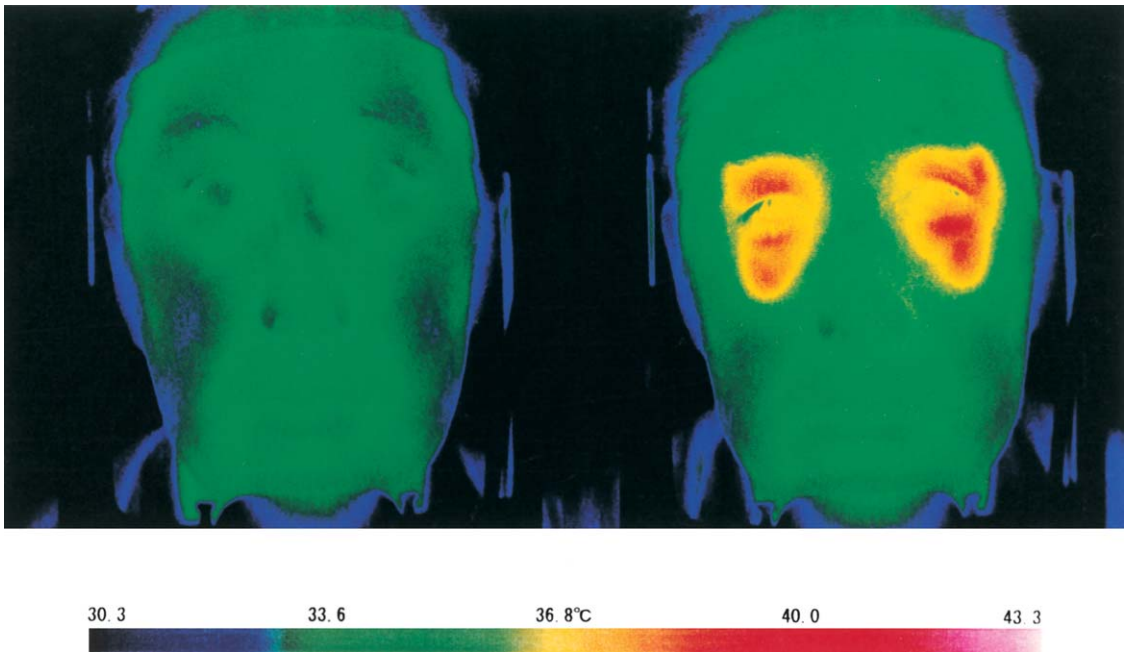

Figure 2. Typical thermogram of eyelids before (left) and after (right) warming with the Eye Warmer, showing an increase in temperature. Red indicates the warmer areas and blue the cooler ones.

Jpn J Ophthalmol
Vol 47: 578–586, 2003

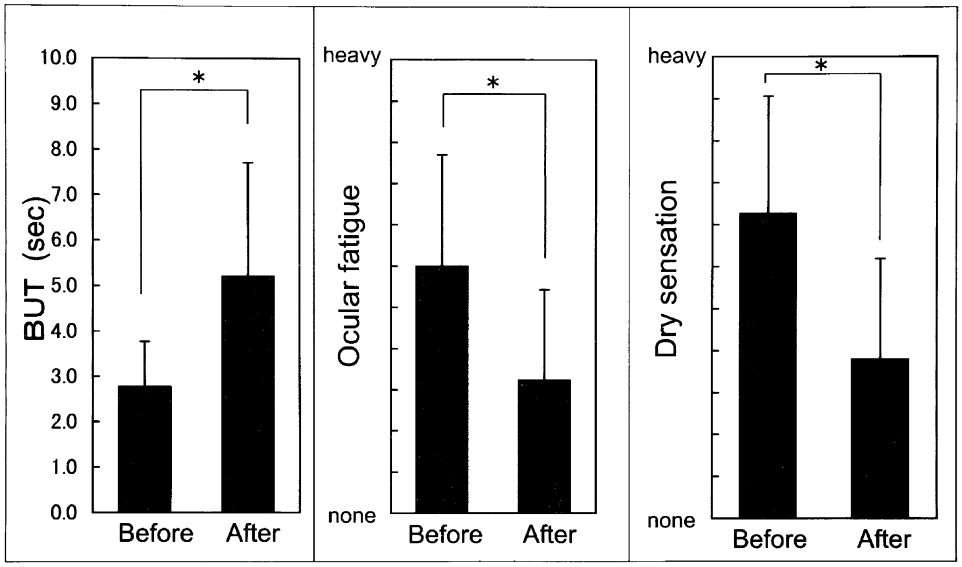

Figure 3. Results for tear break-up time (BUT) and dry-eye symptoms before and after warming with the Eye Warmer, once, for 5 minutes. BUT and the symptoms were significantly improved after treatment compared to before treatment ($P < .01$). Data are shown as means ± SD. *$P < .01$.

The results for BUT and dry-eye symptoms in the two groups before and after the treatment are shown in Figure 5. The BUT value before treatment (2.82 ± 0.87 seconds) significantly increased after treatment (3.82 ± 1.31 seconds) ($P < .01$), and the dry-eye symptoms significantly improved as well ($P < .01$) in the treated group. The mean improvement rates for ocular fatigue and dry sensation were 49.9% ± 35.0% and 56.2% ± 32.3%, respectively. By contrast, there were no significant differences in the results for BUT or ocular fatigue between the first and second examinations in the untreated group. In the treated group, there were positive correlations between the improvement in BUT and rates of improvement in ocular fatigue and dry sensation (correlation coefficient, $r = 0.52$, 0.62, respectively, Figure 6).

The results of assessment of the tear film lipid layer interference patterns and meibomian gland secretion are shown in Table 3. There were no significant differences in distribution between the two groups before treatment. Normal tear film lipid layer interference patterns (grade 1 and grade 2) were noted in 19 eyes (55.9%) before treatment and in 28 eyes (82.4%) after treatment in the treated group. The incidence of normal tear lipid layer was significantly higher after the treatment than before

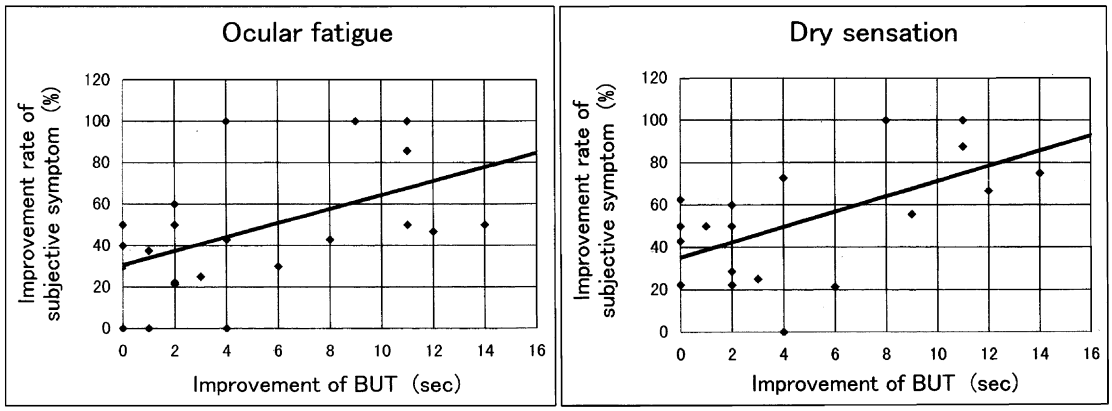

Figure 4. Relationship between the improvement in tear break-up time (BUT) and rates of improvement in symptoms after warming with the Eye Warmer, once, for 5 minutes. There were positive correlations between the improvement in BUT and rates of improvement in ocular fatigue and dry sensation (correlation coefficient, $r = 0.48$, 0.57, respectively).

Table 2. Basic Characteristics of the Ocular Surface, Tear Function, and Meibomian Gland Function Before Treatment in the Treated Group and in the Untreated Group*

Examination	Treated Group (n = 17)	Untreated Group (n = 8)	*P*
Fluorescein	0.68 ± 0.45	0.48 ± 0.44	.16
Rose bengal	1.53 ± 0.97	1.86 ± 1.10	.19
Break-up time	2.82 ± 0.87	2.88 ± 0.81	.84
Cotton thread	12.94 ± 4.75	13.79 ± 5.67	.60
Schirmer test	3.16 ± 1.96	5.19 ± 3.33	.04
Gland dropout	0.82 ± 1.06	1.25 ± 1.13	.20

*Data are shown as means ± SD.

($P = .036$). The incidence of obstruction in meibomian gland orifices (grade 2 and grade 3) was significantly decreased after treatment (14 eyes [41.2%]) compared to before treatment (26 eyes [76.5%]) in the treated group ($P = .006$). By contrast, there were no significant differences in the distribution of grades of tear lipid layer or meibomian gland secretion between the first and second examinations in the untreated group.

No disorders of the eyes were found in the examination by slit-lamp biomicroscopy. There was no decrease in visual acuity, and none of the patients complained of excessive warming of the eye after either study.

Discussion

In this study, we showed the usefulness of this newly developed eyelid-warming device for the treatment of MGD. We previously developed a reliable eye-warming instrument that uses near-infrared radiation.[12] The newly developed device described in this study is disposable, more convenient, and more economical than the earlier device. These benefits enable the patients to continue the treatment indefinitely.

The safety of the Eye Warmer was indicated by measuring the temperature of the eye. Based on animal experiments, lens protein changes that occur at 40ºC can be regarded as the first step in cataract formation.[29,30] Because the temperature of the corneas tested in this study never rose above 38.3ºC, it is unlikely that the Eye Warmer causes lenses to reach 40ºC and develop opacities according to Okuno's model.[31] Our preliminary study had shown that the temperature of the eye decreased substantially within 2 minutes of removing the Eye Warmer. Future work with the Eye Warmer will include study of the monitoring until temperatures return completely to baseline.

Many components of meibomian gland secretions have melting points that are near body temperature, and they solidify when the temperature drops below this level, as occurs in a dilated meibomian acinus or duct.[11] A biochemical shift in the secretions to compounds having higher melting points would also contribute to solidification.[11] In this study, the Eye Warmer raised the temperature of the eyelids above 40ºC, and improved the tear film lipid layer interference pattern, BUT, and meibomian gland secretion. We think that warming the eyelids with

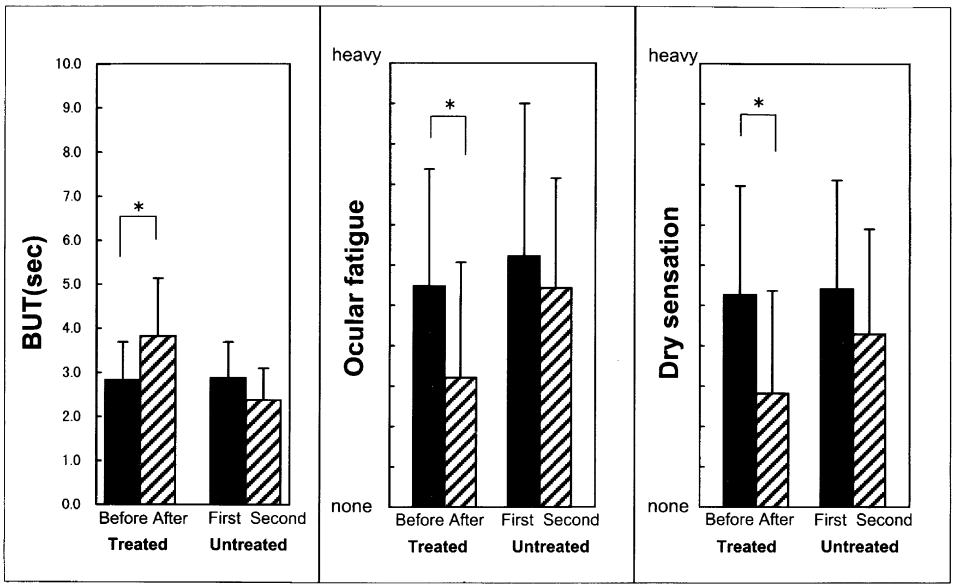

Figure 5. Results for tear break-up time (BUT) and dry-eye symptoms in the treated group and in the untreated group before and after the treatment. BUT and the symptoms were significantly improved after treatment compared to before treatment in the treated group ($P < .01$). By contrast, there were no significant differences in the results for BUT or ocular fatigue between the first and second examinations in the untreated group. *$P < .01$.

Jpn J Ophthalmol
Vol 47: 578–586, 2003

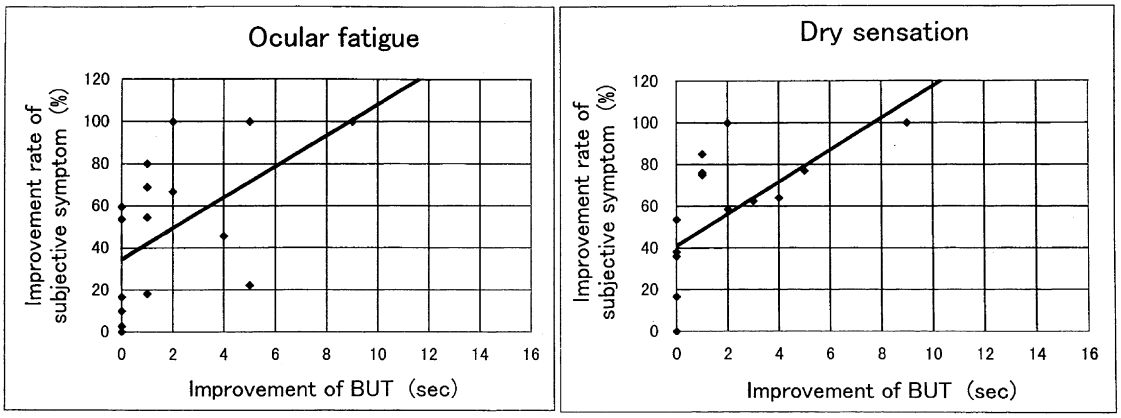

Figure 6. Relationship between the improvement in tear break-up time (BUT) and rates of improvement in symptoms in the treated group. There were positive correlations between the improvement in BUT and rates of improvement in ocular fatigue and dry sensation (correlation coefficient, $r = 0.52$, 0.62, respectively).

the Eye Warmer directly melts solidified meibomian gland lipid and improves tissue metabolism and blood flow by dilating the surrounding blood vessels. The improvements in tissue metabolism and blood flow are thought to improve lipid secretion indirectly. It seems that meibomian gland secretion is not improved with the Eye Warmer in the MGD patients who exhibit severe histologic destruction of meibomian glands. Because most of the MGD patients examined in this study had few dropout glands (data not shown), meibomian gland secretion was improved with the Eye Warmer.

It is reported that the patients with poor lipid secretion exhibited increased tear evaporation and decreased BUT.[32] The Eye Warmer has the advantage for eyelid warming of generating heat and water vapor at the same time. This advantage may improve BUT by increasing secretion of lipid into tears and reducing tear evaporation from the ocular surface. Future assessment of the Eye Warmer will include measurements of tear evaporation from the ocular surface.

A previous study showed that the normal precorneal tear lipid layer is characterized by having a somewhat gray interference color under slit-lamp biomicroscopy.[33] It has also been reported that the colored part of the interference pattern represents a thicker lipid layer than the gray part.[33–35] These studies suggest that eyes showing a grade 3 or 4 pattern before treatment can be regarded as having thicker portions of lipid layers than eyes after treatment. Our hypothesis to explain this condition is: patients with MGD have a stagnant and less dynamic lipid layer resulting in nonuniform distribution of lipid over the aqueous layer, causing thicker parts of the lipid layer to occur. After treatment, the lipid easily and uniformly spreads over the aqueous layer, and the excess lipid not needed to maintain the normal tear film is discharged by the lacrimal puncta.

Table 3. Tear Film Lipid Layer Interference Patterns and Meibomian Gland Secretion in the Treated Group Before and After the Treatment and in the Untreated Group

	Treated Group (n = 17)		Untreated Group (n = 8)	
	Before Treatment (%)	After Treatment (%)	First Examination (%)	Second Examination (%)
Tear lipid layer				
Grade 1	0 (0)	4 (11.8)	0 (0)	0 (0)
Grade 2	19 (55.9)	24 (70.6)	11 (68.8)	9 (56.3)
Grade 3	12 (35.3)	6 (17.6)	4 (25.0)	5 (31.3)
Grade 4	3 (8.8)	0 (0)	1 (6.3)	2 (12.5)
Grade 5	0 (0)	0 (0)	0 (0)	0 (0)
Meibomian gland secretion				
Grade 0	3 (8.8)	9 (26.5)	2 (12.5)	1 (6.3)
Grade 1	5 (14.7)	11 (32.4)	1 (6.3)	2 (12.5)
Grade 2	21 (61.8)	14 (41.2)	7 (43.8)	12 (75.0)
Grade 3	5 (14.7)	0 (0)	6 (37.5)	1 (6.3)

It has been reported that 64.6% of eyes with ocular discomfort are affected by MGD,[3] and this study demonstrated a positive correlation between the improvement in BUT and rates of improvement in dry-eye symptoms. Increasing BUT is thought to be effective in improving the dry-eye symptoms of the MGD patients. Further study is planned to use a similar eye mask without the function of generating heat for the control group to confirm the warming effect.

In the therapeutic study, the measurements were made on the day after the final day on which the Eye Warmer was used. The Eye Warmer was found to be effective even though 12–24 hours had passed since it had last been used. This confirmed that the effect of the Eye Warmer lasts for a certain period after 2 weeks of treatment, but we will also extend the period of examination until the effect of the Eye Warmer disappears.

Warming the eyelids melts the solidified meibomian gland lipid, making it easier to move it by eyelid massage. We expect a combination of the Eye Warmer and eyelid massage to enhance the effectiveness of treatment.

We have demonstrated that the disposable eyelid-warming device can safely and predictably increase eyelid temperature and that it is effective in the treatment of MGD. Warming the eyelids with the Eye Warmer improved the stability and uniformity of the tear lipid layer in MGD patients by melting the meibomian gland lipid. We believe that this device can also be applied to other eyelid diseases, such as multiple chalazia and chronic blepharitis.

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Jpn J Ophthalmol
Vol 47: 578–586, 2003

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