Effect of Eyelid Hygiene Detergent on Obstructive Meibomian Gland Dysfunction

Hirotaka Tanabe, Minako Kaido, Motoko Kawashima, Reiko Ishida, Masahiko Ayaki, and Kazuo Tsubota

1 Department of Ophthalmology, Keio University School of Medicine; 35 Shinanomachi, Shinjuku-ku, Tokyo 160-8582, JAPAN
2 Department of Ophthalmology, Ashikaga Red Cross Hospital; 284-1, Yobecho, Ashikaga, Tochigi, 326-0843, JAPAN
3 Wada Eye Clinic; 2578-27, Hojo, Tateyama, Chiba, 294-0045, JAPAN

† These authors contributed equally to this work.

1 INTRODUCTION

The orifices of the meibomian glands are located on the lid margin surface, and the lipid (meibum) secreted from these glands is supplied to the lid margin and the outermost layer of tears. This lipid serves to enhance the stability of tears, to stimulate tears to extend over the eye surface, to prevent tears from spilling onto the skin at the lid margin and other surfaces, and to prevent tears from evaporating. For example, if the meibomian glands become clogged (obstructed) due to inflammation or infection or if their function decreases, various diseases, including dry eye, hordeolum (commonly referred to as a sty), blepharitis, and meibomitis, which interfere with people’s daily activities, can occur. In fact, 64.6% of patients who visit an ophthalmologist with a chief complaint of symptoms of malaise in their eyes and 86% of patients with dry eye have meibomian gland dysfunction (MGD). Therefore, keeping the lid margin surface clean, including the orifices of the meibomian glands, is extremely important to enhance the glands’ function.

Although several treatment options are available for MGD, they frequently do not exert an immediate effect, and they can often be complicated. Daily lid hygiene has been considered one of the most effective approaches to resolving MGD, and scrubbing the lid margins with baby shampoo using a cotton swab has been recommended. However, these materials were not originally intended for eyelid (one of the most sensitive areas of the body) use.
during which they may also contact the ocular surface; thus, such materials can occasionally be overstimulating or irritating. Lid hygiene shampoo® (Eye Shampoo® MediProduct Co., Ltd., Tokyo, Japan), which is used only for eyelid cleansing, is a new healthcare product that was recently developed in Japan. This product was developed exclusively for lid hygiene and created under the assumption that a mixture of the shampoo and tap water could accidentally enter the eyes. Thus, this shampoo is adjusted to the pH and osmolarity of normal tears and contains certain components that are beneficial to the ocular surface, such as anti-inflammatory substances and moisturizers, based on this idea. Thus far, two Eye Shampoo-related studies have been reported. One study reported the effect of Eye Shampoo on cosmetic-related symptoms, and the other study demonstrated the effect of Eye Shampoo Long, which includes Vitamin D, on lid hygiene and the possibility of eyelash elongation.

In the present study, we investigated the safety and efficacy of Eye Shampoo in normal subjects using tap water as a control. We then conducted the study on MGD patients. At the end of the latter study, we divided the MGD patients into two groups according to the severity of atrophy of the meibomian glands and evaluated differences in the effects of Eye Shampoo between these groups based on various ophthalmologic evaluation items.

### 2 MATERIALS AND METHODS

#### 2.1 Study 1: A pilot study in subjects with normal meibomian glands to assess the safety and efficacy of the shampoo versus tap water control

##### 2.1.1 Study design and target population

Safety and efficacy were verified by evaluating fourteen eyes of 7 subjects (6 males and 1 female aged 28 to 56 years [40.8 ± 11.4 years old]) with normal meibomian glands in the Ophthalmology Department of Keio University Hospital before and after wiping the lid margins using tap water alone at first (control), followed by tap water in combination with lid hygiene shampoo® (Eye Shampoo®) one week later. A questionnaire addressing ocular symptoms (grades 0-100, as assessed via the visual analog scale [VAS]) was administered before and after the treatment. Scores related to ocular conditions, i.e., tear break-up time (TBUT; grades 0-10, the mean of three measurements using fluorescein staining under cobalt blue light from a slit lamp), corneal and conjunctival fluorescein staining scores (grades 0-9; nasal conjunctiva [0-3], cornea [0-3], and temporal conjunctiva [0-3]), lid margin lissamine green staining scores (grades 0-3, Fig. 1), and tear lipid layer interference (grades 1-5, as assessed using a DR-1 tear interference camera [Kowa Co., Nagoya, Japan]) according to the grading system proposed by Yokoi et al., were evaluated. No subject or investigator masking was employed.

This pilot prospective controlled study was registered

| Eye shampoo ingredients | Function |
|-------------------------|----------|
| WATER; AQUA | Solvent |
| POLYGLYCERYL-4 LAURYL ETHER | Surfactant-Cleansing Agent |
| SODIUM CHONDROITIN SULFATE | Conditioning Agent-Humectant |
| SODIUM HYALURONATE | Conditioning Agent-Humectant |
| DIPOTASSIUM GLYCERPHOSPHATE | Conditioning Agent-Humectant |
| ALLANTOIN | Conditioning Agent-Humectant |
| PANTHENOL | Conditioning Agent-Humectant |
| CALCIUM CARBONATE | Buffering Agent |
| SODIUM POLYACRYLATE | Viscosity Increasing Agent |
| SODIUM CHLORIDE | Viscosity Increasing Agent |
| POTASSIUM CHLORIDE | Buffering Agent |
| XANTHAN GUM | Viscosity Increasing Agent |
| PROPALENIOL | Conditioning Agent-Humectant |
| CARBOMER | Viscosity Increasing Agent |
| POTASSIUM HYDROXIDE | pH adjuster |
| HYDROXYPROPYL CYCLODEXTRIN | Emulsion Stabilizer |
| IODOPROPYNYL BUTYLCARBAMATE | Preservative |
| PHENOXYETHANOL | Preservative |
with the University Hospital Medical Information Network Clinical Trial Registry in Japan (UMIN000016906). We adhered to the tenets of the Declaration of Helsinki, and the ethics committee of the Keio University School of Medicine approved the protocol.

2.1.2 Procedure details

Tap water control: The eyelids were washed with tap water for 30 seconds while the eyes were softly closed.

Eye shampoo: The shampoo was pumped onto one hand and gently spread around the eyes. The eyelids were lightly massaged to remove impurities located at the eyelash roots and rinsed with tap water for 30 seconds while the eyes were softly closed.

2.1.3 Statistical Analysis

We used Wilcoxon signed-rank tests to analyze corneal and conjunctival fluorescein/lissamine green/rose bengal staining scores, lid margin lissamine green staining scores, the mucocutaneous junction (MCJ), vascular dilatation, lid margin deformation, plugging, meibum status, subjective symptoms (VAS), and tear lipid layer interference (DR-1).

2.2 Study 2: Safety and efficacy study of lid hygiene shampoo applied to the lid margins in subjects with obstructive meibomian gland dysfunction

2.2.1 Study design and target population

Thirty-four eyes of 34 patients (10 males and 24 females aged 35 to 86 years [68.7 ± 12.1 years old]) who were diagnosed with obstructive MGD at Keio University Hospital and its associated hospital were enrolled in this prospective clinical study in 2014. We determined a diagnosis of MGD in patients (see Fig. 1 for information on our evaluation items for MGD) based on MGD signs. After each patient provided written informed consent, he or she was instructed to cleanse the eyelid margins using lid hygiene shampoo (Eye Shampoo) at least once daily. A questionnaire addressing ocular symptoms (grades 1-5) was administered after the treatment. Scores related to ocular conditions, i.e., TBUT (grades 0-10, the mean of three measurements using fluorescein staining under cobalt blue light from a slit lamp), corneal and conjunctival fluorescein staining scores (grades 0-9; nasal conjunctiva [0-3], cornea [0-3], temporal conjunctiva [0-3]), lid margin lissamine green staining scores (grades 0-3, Fig. 1), the MCJ (grades 0-3, as assessed by fluorescein staining, Fig. 1), vascular dilatation (grades 0-3, Fig. 1), lid margin deformation (grades 0-1, Fig. 1),

![Fig. 1](image-url)
plugging (grades 0-1, Fig. 1), meibum status (grades 0-3, based on the Bron scale), Fig. 1, and tear lipid layer interference (grades 1-5, as assessed using a DR-1 tear interference camera [Kowa Co., Nagoya, Japan] according to the grading system proposed by Yokoi et al.11), were evaluated before and 1 month after initiation of this study. Meibography (using a noninvasive, mobile, pen-shaped meibography system) was also performed on all subjects to determine the morphological characteristics of the meibomian glands before treatment. According to the aggregate meiboscores of the upper and lower lids (suggested by the Arita scale), we classified the subjects into the following groups: normal-mild atrophy or severe atrophy. No subject or investigator masking was employed.

This prospective study was registered with the University Hospital Medical Information Network Clinical Trial Registry in Japan (UMIN000014459). We adhered to the tenets of the Declaration of Helsinki, and the ethics committee of the Keio University School of Medicine approved the protocol.

2.2.2 Procedure details

Eye shampoo: The shampoo was pumped onto one hand and gently spread around the eyes. The eyelids were lightly massaged to remove impurities located at the eyelash roots and rinsed with tap water for 30 seconds while the eyes were softly closed.

2.2.3 Statistical analysis

We used Wilcoxon signed-rank tests to analyze corneal and conjunctival fluorescein/lissamine green/rose bengal staining scores, lid margin lissamine green staining scores, the MCJ, vascular dilatation, lid margin deformation, plugging, meibum status, and tear lipid layer interference. We used Mann–Whitney U tests to analyze subjective symptoms.

3 RESULTS AND DISCUSSION

3.1 The pilot study in subjects with normal meibomian glands to assess safety and efficacy of the shampoo versus tap water control

A significant exacerbating change (p < 0.05) was not detected after either method was applied in terms of the VAS score, TBUT, corneal and conjunctival staining (using fluorescein, lissamine green, and rose bengal), lid margin lissamine green staining, and tear lipid layer interference (as assessed using a DR-1 camera) (Fig. 2a). For VAS scores, foreign body sensation, eye discharge recognition and itchiness were significantly improved only in the group using lid hygiene shampoo (5.5 (0-12.5) to 0 (0-0), p = 0.024; 3 (0-9) to 0 (0-0), p = 0.018; and 0 (0-10.75) to 0 (0-0), p = 0.042, respectively) (Fig. 2b, Table 2). Eyestrain was significantly improved only in the group using tap water alone (23.5 (0-25) to 0 (0-0), p = 0.007) (Fig. 2b, Table 2). No significant differences were observed in other VAS parameters (Table 2).

3.2 Safety and efficacy study of lid hygiene shampoo applied to the lid margins in subjects with obstructive meibomian gland dysfunction

Significant improvements were observed in TBUT, lid margin lissamine green staining scores (upper lids and lower lids), vascular dilatation, and meibum status (3 (2-6) to 6 (4-9.5), p = 0.001; upper lids, 1 (1-2) to 0 (0-1), p = 0.0029; lower lids, 2 (1-3) to 1 (1-1.75), p = 0.0014; 1 (1-2.75) to 1 (0-1), p = 0.0032; and 3 (3-3) to 3 (0-3), p = 0.0066, respectively) (Fig. 3, Table 3). Regarding subjective symptoms, improvements were observed in 27 subjects, and no improvements or aggravation were observed in 7 subjects (Fig. 4, Table 4). Meibography revealed that 28 subjects had normal meibomian glands (based on the aggregate scores of the upper and lower lids) and 6 subjects had meibomian gland atrophy (Table 5). Significant improvements were observed in subjective symptoms (Atrophy(−), 4 (3-4), Atrophy(+) 4 (2-5.4), p = 0.9059; no difference between these two groups) and lid margin lissamine green staining scores (upper lids: Atrophy(−), 1 (1-3) to 1 (0-1), p = 0.0109; Atrophy(+) 1.5 (1-2) to 0.5 (0-1), p = 0.0253; lower lids: Atrophy(−), 2 (1-3) to 1 (1-1.25), p = 0.0089; Atrophy(+) 2 (2-2.75) to 1 (1-1.75), p = 0.0339) in both groups (Fig. 5, Table 6). However, TBUT (Atrophy(−), 2 (2-6) to 6 (4-10), p = 0.0034; Atrophy(+), 4 (3.25-5.5) to 5.5 (5-6), p = 0.0588), vascular dilatation (Atrophy(−), 1 (0.75-2) to 1 (0-1), p = 0.0080; Atrophy(+), 2 (1-3) to 1 (0.25-2.5), p = 0.1797), and meibum status (Atrophy(−), 3 (2.75-3) to 3 (0-3), p = 0.0153; Atrophy(+), 3 (3-3) to 3 (0.75-3), p = 0.1797) improved only in the group with normal meibomian glands (Fig. 5, Table 6). No obvious problems were noted in any of the subjects throughout the study.

In this study, we evaluated the effect of lid hygiene shampoo (Eye Shampoo) on normal subjects and subjects with obstructive MGD and demonstrated its safety and effectiveness. Based on our results, daily lid hygiene with lid hygiene shampoo may be beneficial as part of healthcare routines.

A previous study demonstrated that washing the eyes with tap water alone can cause deterioration of the ocular surface. This concern may reduce the frequency of lid hygiene routines using tap water. In the study, safety was investigated by washing both the inner and outer ocular surfaces with the eyes wide open. In contrast, in our present study, the eyelids were washed with the eyes...
Fig. 2 (a, b) Ocular examination results before and after wiping the lid margins with tap water alone or in combination with lid hygiene shampoo (Eye Shampoo) in subjects with normal meibomian glands. In the box-and-whisker plots, the bottom of the box indicates the first quartile, and the top of the box indicates the third quartile. The band inside the box represents the median. To highlight suspected outliers, the upper whisker is set as the maximum or the third quartile + 1.5 × IQR. The lower whisker indicates the minimum or the first quartile - 1.5 × IQR. The bee swarm plot is a one-dimensional scatter plot with nonoverlapping points. Note that because the placement of the dots in the figures are randomly determined in the bee swarm plot, the dots are sometimes merged. ** Significant improvement; p < 0.05 and * Noted difference; p < 0.1 are demonstrated.
Table 2  Visual analog scale (VAS) parameters before and after cleansing the eyelid margin with tap water alone or in combination with lid hygiene shampoo (Eye Shampoo) in subjects with normal meibomian glands.

| Parameters                      | Water | Lid Hygiene Shampoo |
|---------------------------------|-------|---------------------|
|                                 | Before | After | Before | After |
| Dryness                         | 7      | 0     | 0      | 0     |
| 25%-75%                         | 0-13.625 | 0-8.75 | 0-12   | 0-4.5 |
| P (Wilcoxon signed-rank test)   | 0.078* |       | 0.107  |       |
| Opening difficulty              | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-6.25 | 0-2.25 | 0-0    | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.684  |       | 0.109  |       |
| Foreign body sensation          | 2.5    | 0     | 5.5    | 0     |
| 25%-75%                         | 0-20.5 | 0-5.25 | 0-12.5 | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.216  |       | 0.024**|       |
| Pain                            | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-3    | 0-14  | 0-6.75 | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.462  |       | 0.066* |       |
| Lacrimation                     | 0      | 0     | 3      | 0     |
| 25%-75%                         | 0-4.75 | 0-0   | 0-5.25 | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.683  |       | 0.068* |       |
| Eye discharge                   | 0      | 0     | 3      | 0     |
| 25%-75%                         | 0-4.5  | 0-3   | 0-9    | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.465  |       | 0.018**|       |
| Itchiness                       | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-21.5 | 0-3   | 0-10.75| 0-0   |
| P (Wilcoxon signed-rank test)   | 0.074* |       | 0.042**|       |
| Haziness                        | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-0    | 0-0   | 0-0    | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.715  |       | 0.180  |       |
| Glare                           | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-0    | 0-0   | 0-0    | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.180  |       | 0.102  |       |
| Uncomfortable heaviness         | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-18.75| 0-0   | 0-8.25 | 0-4.5 |
| P (Wilcoxon signed-rank test)   | 0.078* |       | 0.180  |       |
| Eyestrain                       | 23.5   | 0     | 0      | 0     |
| 25%-75%                         | 0-25   | 0-0   | 0-7.5  | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.007**|       | 0.066* |       |
| Smarting pain                   | 0      | 0     | 0      | 0     |
| 25%-75%                         | 0-3.75 | 0-7.5 | 0-7.5  | 0-0   |
| P (Wilcoxon signed-rank test)   | 0.746  |       | 0.066* |       |

** Significant improvement; \( p < 0.05 \)

* Noted difference; \( p < 0.1 \)
closed. Thus, we speculate that the method of washing with tap water may be a key issue. In our controlled study to evaluate the safety and efficacy of wiping the lid margins with tap water alone or in combination with lid hygiene shampoo in subjects with normal meibomian glands, both safety and efficacy, i.e., certain significant subjective improvements, were demonstrated. VAS parameters in the two groups demonstrated that foreign body sensation, eye discharge recognition and itchiness were significantly improved only in the group using lid hygiene shampoo (Fig. 2b, Table 2). Regarding eyestrain, although improvement was observed in both groups, significant improvement was noted only in the group using tap water alone (Fig. 2b, Table 2), which may explain why washing with tap water alone is sufficient to induce certain subjective improvements. Certain differences ($p < 0.1$) in the parameters related to stimulation, i.e., pain, lacrimation and smarting pain, were noted only in the group using lid hygiene shampoo ($0(0-0.75)$ to $0(0-0)$, $p = 0.066$; $0(0-5.25)$ to $0(0-0)$, $p = 0.068$; and $0(0-7.5)$ to $0(0-0)$, $p = 0.066$, respectively) (Table 2). This finding may be related to the special characteristics of the lid hygiene shampoo (specifically, Eye Shampoo), which are adjusted to be similar to those of normal tears (Table 1). Likewise, we must consider all the possible effects of the positive functions of the ingredients in the shampoo (Table 1) on our study results. Humectants (propanediol, dipotassium glycyrrhizate, allantoin, panthenol, sodium chondroitin sulfate, and sodium hyaluronate) may increase TBUT (Fig. 3, Table 3), the pH adjuster (potassium hydroxide) and anti-inflammatory ingredients (dipotassium glycyrrhizate, allantoin, and panthenol) may cause subjects to feel better and ease some symptoms (foreign body sensation, eye discharge recognition and itchiness) (Fig. 2b, Table 2), and the surfactant-cleansing...
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Table 3  Ocular examination results before and after cleansing the eyelid margin with lid hygiene shampoo (Eye Shampoo) at least once daily for 1 month (1-M usage of lid hygiene shampoo) in patients with obstructive MGD.

| Variables                                | Before median (25%, 75%) | After median (25%, 75%) | P (Wilcoxon signed-rank test) |
|------------------------------------------|--------------------------|-------------------------|-----------------------------|
| Tear break-up time                       | 3 (2,6)                  | 6 (4,9.5)               | 0.0010**                    |
| Fluorescein staining score               | 0 (0,1)                  | 0 (0,1)                 | 0.4669                      |
| Lid margin lissamine green staining score| Upper lids 1 (1,2)       | 1 (0,1)                 | 0.0029**                    |
|                                          | Lower lids 2 (1,3)       | 1 (1.1,75)              | 0.0014**                    |
| Vascular dilatation                      | 1 (1,2,75)               | 1 (0,1)                 | 0.0032**                    |
| MCJ                                      | 2 (0,3)                  | 1 (0,3)                 | 0.4593                      |
| Lid margin deformation                   | 0 (0,1)                  | 0 (0,1)                 | NA                          |
| Plugging                                 | 1 (1,1)                  | 1 (0,1)                 | 0.3173                      |
| Meibum properties                        | 3 (3,3)                  | 3 (0,3)                 | 0.0066**                    |

** Significant improvement; p < 0.05

Fig. 4  Subjective symptom change after cleansing the eyelid margin with lid hygiene shampoo (Eye Shampoo) at least once daily for 1 month in patients with obstructive MGD.

Table 4  Subjective symptom change after cleansing the eyelid margin with lid hygiene shampoo (Eye Shampoo) at least once daily for 1 month in patients with obstructive MGD.

|                  | Number | Percentage |
|------------------|--------|------------|
| 1: Aggravation   | 2      | 5.9        |
| 2: No change     | 5      | 14.7       |
| 3: Slight improve| 7      | 20.6       |
| 4: Moderate improve | 14  | 41.1       |
| 5: Drastic improve | 6     | 17.6       |

agent (polyglyceryl-4 lauryl ether) may strengthen the lid hygiene effect of tap water, thus affecting all the data related to the lid hygiene issue.

In the present study, we determined the diagnosis of MGD in patients based on MGD signs (Fig. 1) suggested by a previous report and the International Workshop on Meibomian Gland Dysfunction\(^\text{16, 17}\). We then used meibography (a noninvasive, mobile, pen-shaped meibography system) to detect meibomian gland dropout\(^\text{13, 14}\), which refers to loss of the acinar tissue\(^\text{18, 19}\), and divided the MGD patients into two groups according to the extent of meibomian gland atrophy (Table 5). We subsequently performed a controlled study by evaluating critical parameters in these two groups.

Significant improvements were observed in the lid margin lissamine green staining scores of the upper and lower lids; neither of these of scores depended on the morphological characteristics of the meibomian glands, which were scored using meibography (Fig. 5, Table 6). Lid margin lissamine green staining scores reflect the extent of lid wiper epitheliopathy, where the lid wiper was originally defined as the portion of the marginal conjunctiva of the upper eyelid\(^\text{20}\); later, the importance of the lower eyelid was also demonstrated\(^\text{21}\) in aiding wiping of the ocular surface during blinking. In particular, the extent of lid wiper epitheliopathy is considered to be associated with the level of dry eye\(^\text{20, 22}\). Thus, we classified the lid margin lissamine green staining scores according to the extent of the staining levels of both the upper and lower lid margins (Fig. 1). We hypothesized that a lid hygiene routine including lid hygiene shampoo can remove debris, dead cells or other occlusions from the tracts of the meibomian glands. The openings of these glands are located on the lid margin and allow meibum to move onto the ocular surface more smoothly from the MCJ to the posterior edge, effectively decreasing the extra friction between the inner side of the lid margin and the corneal surface. This mechanism may explain the observed improvements in lid margin lissamine green staining scores, which reflect the extent of lid wiper
Table 5  Meibomian gland atrophy classification (normal-mild atrophy/severe atrophy) according to the aggregate meiboscores of the upper and lower lids using the Arita scale.

| Score | Description | Upper lids | Lower lids |
|-------|-------------|------------|------------|
| 0     | No atrophy  | <1/3       | <1/3       |
| 1     | <1/3 to 2/3 | >2/3       | >2/3       |
| 2     | >2/3        |            |            |

Meibomian gland score (upper row) of the upper or lower lid based on the percentage of gland atrophy (lower row)

Aggregate scores of upper and lower lids ≥5 Atrophy: 6 eyes
Aggregate scores of upper and lower lids <5 Normal: 28 eyes

Fig. 5  Ocular examination results, which were divided into two categories according to the extent of meibomian gland atrophy (with/without) before and after 1-M usage of lid hygiene shampoo (Eye Shampoo) in patients with obstructive meibomian gland dysfunction (MGD). In the box-and-whisker plots, the bottom of the box indicates the first quartile, and the top of the box indicates the third quartile. The band inside the box represents the median. To highlight suspected outliers, the upper whisker is set as the maximum or the third quartile + 1.5 × IQR. The lower whisker indicates the minimum or the first quartile - 1.5 × IQR. The bee swarm plot is a one-dimensional scatter plot with nonoverlapping points. Note that because the placement of the dots in the figures are randomly determined in the bee swarm plot, the dots are sometimes merged. ** Significant improvement; p < 0.05 and * Noted difference; p < 0.1 are demonstrated.

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epitheliopathy. In addition, the improvement in TBUT (to a certain extent, \( p < 0.1 \)) despite the lack of improvement in meibum status may have occurred because the remaining operational meibomian glands were sufficiently functional. In fact, according to a previous report, only 45\% of meibomian glands are required for proper function. However, TBUT, vascular dilatation and meibum status were significantly improved only in the group with normal meibomian glands (Fig. 5, Table 6). These parameters seem to be closely associated. Meibum plays a crucial role in inhibiting evaporation of the tear film, as reflected by a high score for TBUT, and tear stability is necessary to maintain a noninflammatory status.

This study has some limitations. First, although we performed a controlled study on normal subjects, we did not conduct a controlled study on MGD patients. We should have used a control group of MGD patients with untreated eyes. However, the conditions of each eye (right eyes or left eyes) of MGD patients are different; thus, we cannot compare the two eyes within a controlled study in a strict manner. We could perform a controlled study by enrolling only MGD patients with the same level of severity and the same background as a control group; however, adjusting for the severity of MGD is virtually impossible due to the highly diverse characteristics of this condition. Using the same eyes of the same patients as a control during a different term would have also been seriously problematic. Because MGD status involves complex characteristics, if we had used water for lid hygiene in the same eyes before this study, then MGD status would have been altered. Second, in our studies, no subject or investigator masking was employed, which may have allowed the placebo effect to impact the results. Third, we diagnosed MGD according to the MGD signs proposed in previous studies as performed in routine clinical settings. Currently, no absolute diagnostic criteria are available, and we diagnose MGD based on our own standards. This lack of diagnostic criteria may cause differences in the enrollment criteria for MGD patients among various research groups.

**CONCLUSIONS**

In recent years, several lid hygiene products have emerged for the prevention or treatment of ocular diseases in response to changes in modern society, e.g., the prevalence of new eye cosmetics or awareness of the gravity of MGD. Thus, the present time is ideal for the introduction of genuine lid hygiene as a new health routine in the next century. In conclusion, a lid margin cleansing routine that includes lid hygiene shampoo, which targets only eyelid hygiene, may help people maintain their eye health, including subjects with meibomian gland atrophy.

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MediProduct Co., Ltd., provided the lid hygiene shampoo
products for this work but had no involvement in the study design, collection, analysis and interpretation of the data, writing of the manuscript, or the decision to submit the paper for publication. The results of our manuscript were statistically reviewed by a professional data analysis company in Japan (StaGen Co., Ltd.).

CONFLICT OF INTEREST

The patent application for the eyelid margin brush (Application number 2016-024394, Japan) may be applicable in the future (Kazuo Tsubota, Hirotaka Tanabe).

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