# Effect of Using a Combination of Lid Wipes, Eye Drops, and Omega-3 Supplements on Meibomian Gland Functionality in Patients With Lipid Deficient/Evaporative Dry Eye

*Donald R. Korb, OD, Caroline A. Blackie, OD, PhD, Victor M. Finnemore, OD, and Teresa Douglass, AB, COT*

**Purpose:** The aim of this study was to assess the efficacy of using a combination treatment approach consisting of lipid emulsion eye drops, eyelid cleansing wipes, and omega-3 vitamin supplements compared with warm compresses in improving meibomian gland functionality in patients with lipid-deficient/evaporative dry eye disease (LDDE).

**Methods:** This single-center, open-label, investigator-masked, randomized study enrolled patients aged ≥18 years, clinically diagnosed with LDDE defined as having ≤6 functional meibomian glands [meibomian gland yielding liquid secretion (MGYLS)] and positive for dry eye symptoms at screening. Patients were randomized to receive either the combination treatment (lipid emulsion eye drops, omega-3 supplements, and lid hygiene with eyelid wipes) or to apply warm, wet compresses once daily, 8 minutes per day, for 3 months. Meibomian gland functionality (number of MGYLS; primary outcome) and patient-reported subjective assessments (SPEED and OSDI questionnaires; secondary outcomes) were evaluated. Adverse events (AEs) and visual acuity were assessed as safety endpoints.

**Results:** Mean patient age was 41.7 years (n = 26; n = 13 per group). Mean ± SD number of MGYLS was not statistically significantly different between groups at baseline (combination treatment, 3.5 ± 1.5; warm compresses, 4.2 ± 1.4, $P > 0.5$), and was significantly greater with combination treatment versus warm compresses after 3 months of treatment (9.3 ± 2.7 vs. 4.7 ± 2.3; $P = 0.006$). Dry eye symptoms were significantly improved in both groups at all follow-up visits. Two AEs unrelated to treatment were reported; the BCVA was unchanged from baseline in both groups.

**Conclusions:** The combination treatment regimen resulted in significant improvement in meibomian gland functionality and dry eye symptoms. No safety issues were observed.

**Key Words:** meibomian gland dysfunction, dry eye, blepharitis, Systane Balance, warm compresses, ocular surface disease

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The 2011 International Workshop on Meibomian Gland Dysfunction (MGD) concluded that "Meibomian gland dysfunction may well be the leading cause of dry eye disease throughout the world."[1,2] This statement is corroborated by a study showing that the most common form of dry eye is evaporative and that 86% of patient with dry eye have MGD.[3] Furthermore, the prevalence of MGD for adults in the general population has been reported to range from 30.5% to 68.3%.[4,5]

MGD is characterized by reduced gland function [ie, decreased volume of liquid secretion or decreased number of meibomian glands yielding liquid secretion (MGYLS) under the forces of deliberate blinking] and/or an altered gland structure (partial or complete gland drop out).[6,7] The lipid component of the tear film, which is produced by the meibomian glands, contributes to tear film stability and reduces evaporation of the tear film. The primary cause of aqueous deficient dry eye is reduced lacrimal function, whereas the primary cause of lipid-deficient dry eye (LDDE) is MGD.[8] Although both forms may occur together, one can definitively diagnose the presence of either disease by specifically measuring lacrimal and meibomian gland function individually.[9]

Symptoms of dry eye include burning, tearing, symptoms of mechanical etiology and ocular discomfort, and vary in incidence and severity among individual patients.[9,10] Although patient-reported symptoms and objective signs of dry eye often do not correlate,[10,11] the number of functional meibomian glands (MGYLS) has been reported to correlate significantly with dry eye symptoms.[7] Since its introduction in 2008, standardized evaluation of meibomian gland function, using a standardized force approximating the forces of a deliberate blink, has become a critical metric for both investigative studies and clinical practice.[2,7]

The standard of care for treating patients with MGD is daily use of warm wet compresses. This regimen increases the temperature of meibomian glands with the intended goal

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From the Korb Associates, Boston, MA.

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Reprints: Caroline A. Blackie, OD, PhD, 400 Commonwealth Ave, Unit #2, Boston, MA 02215 (e-mail: cblackie@tearscience.com).

being to liquefy obstructed material in the gland and allow free flow of meibomian gland oil into the tear film, leading to increased tear film lipid layer thickness.[12] However, as noted by the International Workshop on Meibomian Gland Dysfunction, "Warm compress therapy is a commonly recommended but poorly standardized treatment for MGD that is performed by patients for variable durations of heat application and with varying compliance."[13] The workshop subsequently recommended including lipid emulsion eye drops, lid hygiene, and increased omega-3 fatty acid intake in regimens for managing MGD.[13]

Use of lipid emulsion eye drops to restore components of the tear film and administration of a lid hygiene regimen (eg, lid scrubs and massage) have been shown to increase lipid layer thickness and tear film break-up time in patients with MGD.[14–16] In separate studies, oral supplements containing antiinflammatory omega-3 fatty acids have been shown to increase tear film stability in patients with MGD[16] and have been hypothesized to reduce inflammation-associated ocular tissue damage associated with dehydration of the tear film.[17,18]

The aim of this study was to assess the efficacy of using a combination treatment regimen consisting of lipid emulsion eye drops, eyelid cleansing wipes, and omega-3 vitamin supplements, as suggested by the International Workshop on MGD,[1] versus the standard of care (warm compresses), in improving meibomian gland functionality and alleviating symptoms in patients with LDDE.[13]

## MATERIALS AND METHODS

### Study Design

This was a 3-month, prospective, investigator-masked, open-label, randomized, active-controlled, single-center study conducted in the United States (ClinicalTrials.gov identifier: NCT01733745). Patients provided written informed consent before screening. The study protocol and informed consent forms were reviewed and approved by an ethics committee. The study was conducted under the approval of an Institutional Review Board, and all tenets of the Declaration of Helsinki and Good Clinical Practice guidelines were strictly observed.

The study consisted of 4 visits: the screening/baseline visit and follow-up visits conducted after 1, 2, and 3 months of treatment. After screening, eligible patients were randomly assigned to either the combination treatment group or the warm compresses treatment group.

### Patients

Eligible patients were aged ≥18 years and had an existing clinical diagnosis of LDDE based on the following characteristics: having 6 of fewer functioning lower lid meibomian glands (≤6 MGYLS) and also symptomatic for dry eye [Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire[19] score ≥6 to ≤14]. Patients were also required to have a best-corrected visual acuity (BCVA, Snellen) of 20/40 or better in each eye. Patients were required to discontinue all other MGD management before screening and throughout the study. Key exclusion criteria included ocular or systemic medical conditions that could, in the opinion of the investigator, preclude study participation; ocular or intraocular surgery or serious ocular trauma in either eye ≤6 months before screening; intolerance or hypersensitivity to any component of the study medications; epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella disease of the cornea/conjunctiva, or bacterial/fungal or mycobacterial infection/disease of the eye; use of contact lenses ≤1 week before screening; concomitant use of topical ocular medications during the study; and use of systemic medications that may contribute to dry eye without being on a stable dosing regimen for ≥30 days before screening and throughout the study. Women who were pregnant, may have become pregnant, or were breastfeeding at the time of screening for the study were also excluded. Enrollment of investigator's office staff, relatives, or members of their respective households and enrollment of >1 member of the same household were prohibited.

### Treatment

#### Combination Treatment Group

In accordance with the manufacturer's instructions and prior reports on various therapies,[14–18,20] patients in the combination treatment group self-administered lid hygiene with hypoallergenic eyelid cleansing wipes (Systane Lid Wipes; Alcon Laboratories, Inc, Fort Worth, TX) once daily; instilled 1 drop of lipid emulsion eye drops formulated to restore lipid, aqueous, and mucin components of the tear film (Systane Balance; Alcon) 4 times daily; and took 2 oral vitamin supplements containing 1000 mg of omega-3 fatty acids (Systane Vitamin Omega-3 Healthy Tears; Alcon) daily for 3 months.

#### Warm Compress Group

Patients in the warm compresses group applied a warm wet microfiber compress (from Terry World Textiles, LLC, Santa Monica, CA) to both eyelids for 8 minutes once daily for 3 months. Patients were provided with and instructed to use a clean cloth every day. They were instructed to wet the washcloth with water that was at the maximum comfortable temperature and to squeeze out excess water before placing the warmed cloth over their closed eyes. They were instructed to maintain a bowl of hot water beside them to rewet the washcloth when it began to cool (approximately every 2 minutes). They were instructed to double-fold the cloth, for the cloth to retain the heat for as long as possible.

Ophthalmic examination and adverse events (AEs), best-corrected visual acuity (BCVA), Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, Ocular Surface Disease Index (OSDI) questionnaire, presence of itching, lid status, meibography, and meibomian gland functionality assessments were conducted at screening and all follow-up visits.

### Endpoints

The primary efficacy endpoint was meibomian gland functionality, assessed by standardized diagnostic meibomian gland expression to determine the number of MGYLS. The

technique and instrumentation used for the standardized assessment of meibomian gland function have been reported elsewhere.[7] Briefly, the meibomian gland evaluator (TearScience, Inc, Morrisville, NC) applies force over the meibomian glands that approximate the force experienced by the glands during a deliberate blink. The results provide information as to the natural functional state of the meibomian glands during deliberate blinking.

Secondary efficacy endpoints were ocular symptoms and dry eye symptoms, which were assessed with the OSDI and SPEED questionnaires, respectively. Both questionnaires have been validated to reliably capture dry eye symptoms and have been used in many studies.[18,19] The OSDI questionnaire assesses symptoms over the previous week, whereas the SPEED questionnaire assess symptoms over the previous 3 months. The OSDI does not include severity of symptoms in the assessment, but it does include contexts in which symptoms may be exacerbated. The SPEED questionnaire includes frequency and severity of symptoms but does not contain context-based questions. The OSDI has a total score range of 0 to 100. The total score range of the SPEED questionnaire is 0 to 28.

Lid status assessment included the following: (1) A semiquantitative assessment of the presence and degree of collarettes and/or debris on the epidermis or eyelashes. This was graded according to the standard clinical scale of "absent, mild, moderate, and severe." (2) The presence and degree of itching and eye rubbing. These were recorded similarly as "absent, mild, moderate, or severe." and (3) Meibography was performed using the Modi Topographer (Veatch Instruments, Phoenix, AZ) and analyzed using the Phoenix software provided. Meibography was used to assess the percentage of partial meibomian glands. Results were graded by a single trained masked observer using a scale from 1 (no gland drop out) to 4 (>75% gland drop out). Safety endpoints were assessed by recording AEs during the study and BCVA at each study visit.

## Statistical Analysis

Assuming a treatment difference in meibomian gland functionality score of 1 and an SD of 0.8, it was determined that a total of 26 subjects (52 eyes) would yield ~90% power with a 5% level of significance. The primary outcome, superiority in meibomian gland functionality, was assessed at 3 months. Right and left eyes were pooled and treated as independent cases for meibomian gland functionality, itching/eye rubbing, lid status, and meibography endpoints. Gland functionality (ie, number of MGYLS), SPEED questionnaire scores, and OSDI questionnaire scores were analyzed by analysis of variance (ANOVA) with treatment group as a factor, baseline value as a covariable, and treatment by baseline value as an interaction. Meibography scores were analyzed using Cochran–Mantel–Haenszel tests. Lid status, itching/eye rubbing, BCVA, and AEs were summarized descriptively.

# RESULTS

## Patients

A total of 26 patients (mean ± SD age, 41.7 ± 19.8 years; range, 18−72 years) were screened and randomized (combination treatment group, n = 13; warm compresses group, n = 13); all patients completed the study. The majority of patients were women (n = 21/26, 80.8%) and of white ethnicity (n = 23/26, 88.5%). There were no statistically significant differences in demographic data between groups.

## Efficacy Outcomes

At baseline, the mean ± SD numbers of MGYLS in the combination treatment and warm compresses groups were 3.5 ± 1.5 and 4.2 ± 1.4, respectively. In the combination treatment group, the number of MGYLS increased significantly from baseline at all follow-up visits. In the warm compresses group, the number of MGYLS was not statistically significantly different from baseline. The number of MGYLS was significantly higher in the combination treatment group compared with the warm compresses group at month 2 [6.4 ± 2.5 vs. 3.5 ± 1.9; $P = 0.0365$; least squares (LS) mean between-group difference = 3.1] and month 3 (9.3 ± 2.7 vs. 4.7 ± 2.3; $P = 0.0061$; LS mean difference = 5; Fig. 1).

Mean SPEED scores were decreased from baseline at months 1, 2, and 3 in both treatment groups (Table 1); differences between groups were not statistically significant. At month 3, SPEED scores were decreased from baseline by 55% in the combination treatment group and by 29% in the warm compresses group (change from baseline, $P = 0.0249$, ANOVA). Mean OSDI scores were significantly improved from baseline at months 1, 2, and 3 ($P < 0.0001$ at all time points, ANOVA; Table 1); mean OSDI scores were not significantly different between groups. At month 3, OSDI scores were reduced from baseline by 55% in the combination treatment group and by 33% in the warm compresses group (Table 1), with the mean OSDI scores in both treatment groups improving from the clinical classification[18] of moderate dry eye at baseline to mild dry eye after 3 months of treatment.

## Exploratory Outcomes

The presence and severity of itching and eye rubbing were improved from baseline in both the combination

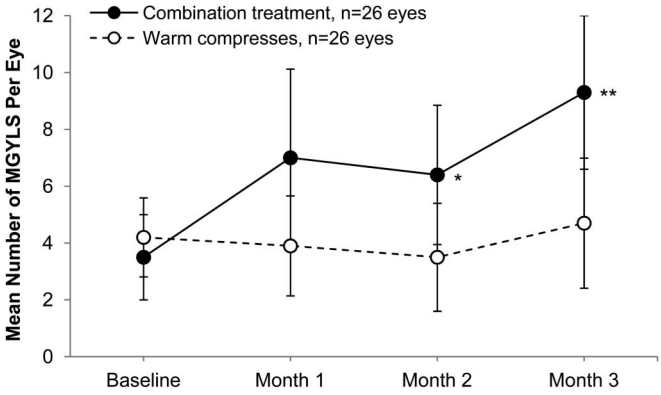


**FIGURE 1.** Meibomian gland functionality. Left and right eyes were taken as independent cases. *$P < 0.05$ and **$P < 0.01$ for combination treatment versus warm compresses. Error bars represent SDs. MGYLS, meibomian glands yielding liquid secretion.

**TABLE 1.** Patient-Reported Dry Eye and Ocular Symptoms

| | Combination Treatment (n = 13) | Warm Compresses (n = 13) | P* |
|---|---|---|---|
| SPEED questionnaire scores, mean ± SD† | | | |
| Baseline | 11.2 ± 2.6 | 11.2 ± 2.0 | NA |
| Month 1 | 8.2 ± 3.2 | 9.5 ± 3.9 | 0.2585 |
| Month 2 | 6.5 ± 3.0 | 7.9 ± 4.3 | 0.0745 |
| Month 3 | 5.0 ± 3.4 | 7.9 ± 4.5 | 0.0249 |
| OSDI questionnaire scores, mean ± SD‡ | | | |
| Baseline | 32.3 ± 12.8 | 26.9 ± 15.4 | N/A |
| Month 1 | 22.6 ± 10.5 | 21.0 ± 16.3 | <0.0001 |
| Month 2 | 16.1 ± 9.6 | 19.7 ± 17.4 | <0.0001 |
| Month 3 | 14.4 ± 10.2 | 17.9 ± 18.6 | <0.0001 |

*P values assessed for change from baseline values using ANOVA with baseline as a covariable.
†Possible score range, 0 (best) to 28 (worst).
‡Possible score range, 0 (best) to 100 (worst).
NA, not applicable; SPEED, Standard Patient Evaluation of Eye Dryness.

**TABLE 2.** Presence of Itching and Eye Rubbing

| | Eyes, n (%)* | |
|---|---|---|
| | Combination Treatment (n = 26) | Warm Compresses (n = 26) |
| Itching | | |
| Baseline | | |
| Not present | 4 (15.4) | 14 (53.8) |
| Mild | 18 (69.2) | 10 (38.5) |
| Moderate | 2 (7.7) | 2 (7.7) |
| Severe | 2 (7.7) | 0 |
| Month 1 | | |
| Not present | 20 (76.9) | 10 (38.5) |
| Mild | 0 | 14 (53.8) |
| Moderate | 4 (15.4) | 2 (7.7) |
| Severe | 2 (7.7) | 0 |
| Month 2 | | |
| Not present | 18 (69.2) | 16 (61.5) |
| Mild | 6 (23.1) | 10 (38.5) |
| Moderate | 2 (7.7) | 0 |
| Severe | 0 | 0 |
| Month 3 | | |
| Not present | 22 (84.6) | 18 (69.2) |
| Mild | 4 (15.4) | 8 (30.8) |
| Moderate | 0 | 0 |
| Severe | 0 | 0 |
| Eye rubbing | | |
| Baseline | | |
| Not present | 2 (7.7) | 4 (15.4) |
| Mild | 12 (46.2) | 10 (38.5) |
| Moderate | 10 (38.5) | 12 (46.2) |
| Severe | 2 (7.7) | 0 |
| Month 1 | | |
| Not present | 10 (38.5) | 6 (23.1) |
| Mild | 12 (46.2) | 20 (76.9) |
| Moderate | 4 (15.4) | 0 |
| Severe | 0 | 0 |
| Month 2 | | |
| Not present | 14 (53.8) | 16 (61.5) |
| Mild | 10 (38.5) | 10 (38.5) |
| Moderate | 2 (7.7) | 0 |
| Severe | 0 | 0 |
| Month 3 | | |
| Not present | 18 (69.2) | 12 (46.2) |
| Mild | 6 (23.1) | 12 (46.2) |
| Moderate | 2 (7.7) | 2 (7.7) |
| Severe | 0 | 0 |

*Left and right eyes were treated as independent samples.

treatment group and the warm compresses group (Table 2). The presence and severity of collarettes and/or debris on the epidermis or eyelashes was improved from baseline in both the combination treatment group and the warm compresses group (Table 3, Fig. 2).

Meibography scores were statistically unchanged from baseline at all follow-up visits in both treatment groups. In the combination treatment group at both baseline and month 3, 16 eyes (61.5%) had 1% to 24% partial glands and 10 eyes (38.5%) had 25% to 75% partial glands. In the warm compresses group at both baseline and month 3, 3 eyes (11.5%) had no partial glands, 12 eyes (46.2%) had 1% to 24% partial glands, and 11 eyes (42.3%) had 25% to 75% partial glands. Differences between treatment groups were not significant at any visit.

## Safety Outcomes

A total of 2 AEs (infectious mononucleosis and sinusitis) were reported for a single patient in the combination treatment group; neither was considered to be treatment related. No serious AEs occurred. Mean BCVA was not statistically different between groups at baseline (combination treatment, 0.0 logMAR; warm compresses, 0.0 logMAR; n = 26 eyes per group) and or at any other point throughout the study.

# DISCUSSION

Daily use of warm moist compresses to liquefy the lipid secretions and obstruction of the meibomian glands is the standard of care for managing MGD and LDDE.[11,12] However, a major concern with at-home compress use is that lack of standardization in terms of application and heat of compress. The goal of this study was to assess the effectiveness of combination treatment with lipid emulsion eye drops, lid hygiene wipes, and omega-3 supplements versus warm compresses on meibomian gland functionality in patients with LDDE, as per the suggestion of the International Workshop on MGD.[1,13]

The results of this study demonstrated that the meibomian gland function was significantly increased from baseline at all follow-up visits in the combination treatment group and was significantly higher by approximately 2-fold in the

**TABLE 3.** Lid Status by Visit

| | Eyes With Collarettes or Desquamated Debris on the Epidermis or Eyelashes, n (%)* | | | | | |
|---|---|---|---|---|---|---|
| | Combination Treatment (n = 26) | | | Warm Compresses (n = 26) | | |
| | Epidermis | Lashes | Collarettes | Epidermis | Lashes | Collarettes |
| Baseline | | | | | | |
| Not present | 4 (20.0) | 4 (20.0) | 8 (40.0) | 4 (16.0) | 9 (36.0) | 7 (28.0) |
| Mild | 14 (70.0) | 14 (70.0) | 9 (45.0) | 16 (64.0) | 14 (56.0) | 16 (64.0) |
| Moderate | 2 (10.0) | 2 (10.0) | 3 (15.0) | 5 (20.0) | 2 (8.0) | 2 (8.0) |
| NA | 6 | 6 | 6 | 1 | 1 | 1 |
| Month 1 | | | | | | |
| Not present | 4 (33.3) | 2 (16.7) | 6 (50.0) | 12 (57.1) | 6 (28.6) | 5 (23.8) |
| Mild | 8 (66.7) | 10 (83.3) | 4 (33.3) | 9 (42.9) | 13 (61.9) | 12 (57.1) |
| Moderate | 0 | 0 | 2 (16.7) | 0 | 2 (9.5) | 4 (19.0) |
| NA | 14 | 14 | 14 | 5 | 5 | 5 |
| Month 2 | | | | | | |
| Not present | 4 (50.0) | 4 (50.0) | 6 (75.0) | 13 (61.9) | 9 (42.9) | 5 (23.8) |
| Mild | 4 (50.0) | 4 (50.0) | 2 (25.0) | 8 (38.1) | 12 (57.1) | 16 (76.2) |
| Moderate | 0 | 0 | 0 | 0 | 0 | 0 |
| NA | 18 | 18 | 18 | 5 | 5 | 5 |
| Month 3 | | | | | | |
| Not present | 5 (100.0) | 3 (60.0) | 2 (40.0) | 14 (87.5) | 10 (62.5) | 2 (12.5) |
| Mild | 0 | 2 (40.0) | 3 (60.0) | 2 (12.5) | 6 (37.5) | 11 (68.8) |
| Moderate | 0 | 0 | 0 | 0 | 0 | 3 (18.8) |
| NA | 21 | 21 | 21 | 10 | 10 | 10 |

*Left and right eyes were treated as independent samples; percentages were calculated based on total number of eyes with evidence of collarettes or debris on epidermis or lashes (ie, excluding NA values).

combination treatment group compared with the warm compress control group at months 2 and 3. Patient-reported dry eye and ocular symptoms, as reflected by SPEED and OSDI questionnaire scores, were significantly improved from baseline at all follow-up visits in both treatment groups. Score reductions were larger in the combination treatment versus the warm compresses group for both questionnaires. Patient-reported itching and eye rubbing were also improved from baseline in both treatment groups. After 3 months of treatment, collarettes or desquamated debris on the epidermis or eyelashes were evident on <20% of eyes that received combination treatment compared with >60% of eyes treated with warm compresses. This clinically significant greater improvement in the combination therapy as compared with the warm compress therapy is to be expected given that the warm compress treatment offered no mechanical removal of lash debris.

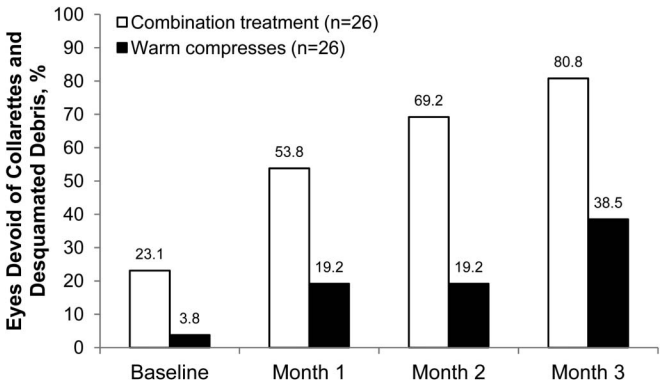


**FIGURE 2.** Lid status. Left and right eyes were taken as independent cases. Percentages of eyes per group are indicated above bars.

The presence of partial or truncated meibomian glands, indicating gland atrophy, was unchanged from baseline in both treatment groups. Both treatments were well tolerated by patients. No treatment-related AEs occurred, and there were no study discontinuations.

The relationship between the number of functional meibomian glands and dry eye symptoms scores has been previously documented.[7] In this study, the number of functional glands at month 3 was significantly improved in the combination treatment group compared with the warm compresses group. This result is somewhat surprising given prior reports indicating the benefit of warm compress used in this regard. However, the warm compresses in this study were not standardized in that the heat of the compresses, and the precise method of compress application was not controlled. In so far as the combination treatment was to be compared with optimal warm compress use, this is a weakness of the study. However, the study was designed to reflect the standard of care: The majority of warm compresses that are prescribed in a nonstandardized fashion in terms of heat and the method of application. The benefits of the combination treatment remain convincing, indicating that combination treatment has the ability to significantly improve gland function, reduce dry eye symptoms, and promote eyelid margin health.

The open-label design of this trial, which may have introduced patient bias, is a limitation of this study. Although it is known that each of the individual treatments (ie, lipid eye drops, eyelid wipes, or omega-3 supplements) all have positive impact on ocular surface comfort, meibomian gland function, and lid margin health,[14–18,20] this study does not show which of the individual treatments had the largest impact on outcomes. What is clear is that the impact of a combined approach is highly significant and worthy of consideration for patients at risk for ocular surface disease and MGD, particularly, because many of these patients with MGD have coexisting blepharitis and where MGD is chronic and progressive.[1,2,13]

In summary, meibomian gland functionality was significantly improved in patients with LDDE who used combination treatment compared with those who used warm compresses. Patient-reported dry eye symptoms and ocular discomfort as well as itching and eye rubbing were improved from baseline in both treatment groups, and no treatment-related AEs were reported with either treatment.

## REFERENCES


1. Nichols KK, Foulks GN, Bron AJ, et al. The international workshop on meibomian gland dysfunction: executive summary. *Invest Ophthalmol Vis Sci.* 2011;52:1922–1929.
2. International Dry Eye WorkShop Report of the International Dry Eye WorkShop (DEWS). *Ocul Surf.* 2007;5:61–204.
3. Lemp MA, Crews LA, Bron AJ, et al. Distribution of aqueous-deficient and evaporative dry eye in a clinic-based patient cohort: a retrospective study. *Cornea*. 2012;31:472–478.
4. Siak JJ, Tong L, Wong WL, et al. Prevalence and risk factors of meibomian gland dysfunction: the Singapore Malay eye study. *Cornea*. 2012;31:1223–1228.
5. Jie Y, Xu L, Wu YY, et al. Prevalence of dry eye among adult Chinese in the Beijing Eye Study. *Eye (Lond).* 2009;23:688–693.
6. Nelson JD, Shimazaki J, Benitez-del-Castillo JM, et al. The international workshop on meibomian gland dysfunction: report of the definition and classification subcommittee. *Invest Ophthalmol Vis Sci.* 2011;52:1930–1937.
7. Korb DR, Blackie CA. Meibomian gland diagnostic expressibility: correlation with dry eye symptoms and gland location. *Cornea*. 2008; 27:1142–1147.
8. Bron AJ, Yokoi N, Gafney E, et al. Predicted phenotypes of dry eye: proposed consequences of its natural history. *Ocul Surf.* 2009;7:78–92. Review.
9. Nichols KK, Mitchell GL, Zadnik K. The repeatability of clinical measurements of dry eye. *Cornea*. 2004;23:272–285.
10. Shimazaki-Den S, Dogru M, Higa K, et al. Symptoms, visual function, and mucin expression of eyes with tear film instability. *Cornea*. 2013;32: 1211–1218.
11. Sullivan BD, Crews LA, Messmer EM, et al. Correlations between commonly used objective signs and symptoms for the diagnosis of dry eye disease: clinical implications. *Acta Ophthalmol.* 2014;92: 161–166.
12. Olson MC, Korb DR, Greiner JV. Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye Contact Lens.* 2003;29:96–99.
13. Geerling G, Tauber J, Baudouin C, et al. The international workshop on meibomian gland dysfunction: report of the subcommittee on management and treatment of meibomian gland dysfunction. *Invest Ophthalmol Vis Sci.* 2011;52:2050–2064.
14. Scaffidi RC, Korb DR. Comparison of the efficacy of two lipid emulsion eyedrops in increasing tear film lipid layer thickness. *Eye Contact Lens.* 2007;33:38–44.
15. Paugh JR, Knapp LL, Martinson JR, et al. Meibomian therapy in problematic contact lens wear. *Optom Vis Sci.* 1990;67:803–806.
16. Sindt CW, Foulks GN. Efficacy of an artificial tear emulsion in patients with dry eye associated with meibomian gland dysfunction. *Clin Ophthalmol.* 2013;7:1713–1722.
17. Baudouin C. The pathology of dry eye. *Surv Ophthalmol.* 2001;45:S211–S220.
18. Miller KL, Walt JG, Mink DR, et al. Minimal clinically important difference for the ocular surface disease index. *Arch Ophthalmol.* 2010; 128:94–101.
19. Ngo W, Situ P, Keir N, et al. Psychometric properties and validation of the Standard Patient Evaluation of Eye Dryness questionnaire. *Cornea*. 2013;32:1204–1210.
20. Olenik A, Jimenez-Alfaro I, Alejandre-Alba N, et al. A randomized, double-masked study to evaluate the effect of omega-3 fatty acids supplementation in meibomian gland dysfunction. *Clin Interv Aging.* 2013;8:1133–1138.