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Authors
Satjawatcharaphong, Pam
Ge, Shaokui
Lin, Meng C

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ORIGINAL ARTICLE

Clinical Outcomes Associated with Thermal Pulsation System Treatment

Pam Satjawatcharaphong*, Shaokui Ge†, and Meng C. Lin‡

ABSTRACT

Purpose. To identify patient characteristics at a baseline ocular surface evaluation that correlate with improvement in dry eye symptoms at a follow-up visit after treatment with the LipiFlow Thermal Pulsation System.

Methods. Thirty-two patients completed a comprehensive baseline ocular surface evaluation and were treated with the LipiFlow Thermal Pulsation System followed by maintenance home therapy. Lipid layer thickness and blink pattern were determined using the LipiView Interferometer. Noninvasive tear breakup time was measured using a Medmont E300 Corneal Topographer. Slit lamp biomicroscopy was used to evaluate invasive tear breakup time and corneal staining after instillation of fluorescein dye. Conjunctival staining, location of the line of Marx, and presence of lid wiper epitheliopathy were evaluated with lissamine green dye. Meibomian gland expressibility was scored using the TearScience Meibomian Gland Evaluator, and meibography was imaged using the Oculus Keratograph. A logistic regression model was used to estimate the odds ratios for having a decreased posttreatment score (reduced symptoms) of Standard Patient Evaluation of Eye Dryness (SPEED).

Results. Baseline SPEED score ($p = 0.01$) and sex ($p = 0.03$) had significant odds ratios at the $\alpha = 0.05$ level. Baseline noninvasive tear breakup time ($p = 0.07$), number of grade 0 meibomian glands in the lower lid ($p = 0.09$), and conjunctival staining grade in the inferior region ($p = 0.10$) met an $\alpha = 0.10$ criterion for significant odds ratios, but not the typical $\alpha = 0.05$ criterion. Higher baseline SPEED score and male sex had greater odds for decreased posttreatment SPEED score.

Conclusions. Our results identified factors that better select candidates for LipiFlow Thermal Pulsation System.
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Key Words: dry eye, meibomian gland dysfunction, sex, thermal pulsation, meibomian gland expression, conjunctival staining, corneal staining, SPEED

Meibomian gland dysfunction (MGD) has been identified as the most prevalent cause of dry eye symptoms.[1] It has been described as a chronic, diffuse abnormality of the meibomian glands (MGs), commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion.[2] The LipiFlow Thermal Pulsation System (Tear Science Inc, Morrisville, NC) is a novel treatment of MGD that was approved by the Food and Drug Administration in 2011. The objective of the device is to apply heat at a controlled temperature directly to the palpebral conjunctiva adjacent to the MGs, while concurrently using a pulsating, massaging pressure to evacuate blocked glands.[3,4] A normal eye houses about 30 and 25 MGs in the upper and lower eyelids, respectively, with gland orifices lying along the eyelid margin.[5] In 1961, Linton et al.[6] postulated that the mechanism of excretion of the MGs was related to the action of blinking and contraction of the orbicularis oculi muscle, which compressed the tarsal plate. This natural milking action of the eye muscles during the blink has served as a basis for development of the LipiFlow System.[7–9]

The device has been described in the literature as a safe alternative to traditional home therapy, such as warm compresses, digital massage, and eyelid scrubs.[10–13] These studies yielded overall positive results and reported reductions in dry eye symptoms persisting from 1 to 12 months; however, only one study used a control group and found LipiFlow to be equally effective to twice daily lid warming and massage.[12] Given the high cost to

*OD, FAAO
†PhD
‡OD, PhD, FAAO
School of Optometry, University of California, Berkeley, Berkeley, California (all authors); Clinical Research Center, University of California, Berkeley, Berkeley, California (MCL); and Vision Science Program, University of California, San Francisco, San Francisco, California (MCL).

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perform the LipiFlow procedure compared with traditional home therapy, any information guiding patient selection could be very useful. The objective of this article was not to determine the efficacy of the LipiFlow treatment compared with home therapy but to identify which ocular characteristics assessed during an initial evaluation of potential LipiFlow candidates correlate with successful outcomes (i.e., reduced symptoms after treatment) and to determine the degree of improvement in these clinical signs and symptoms after a single LipiFlow treatment.

METHODS

Patient Selection

Patients evaluated for this analysis were those seeking LipiFlow treatment from the Ocular Surface Imaging Clinic at the University of California, Berkeley. Eligibility criteria for data analysis were as follows:

Inclusion:

1. Eighteen years or older;
2. Determined to have dry eye signs and symptoms secondary to MGD;
3. Able to complete an initial evaluation and a follow-up visit after treatment.

Exclusion:

1. Determined to have dry eye symptoms that were not secondary to MGD;
2. Had corneal curvature steeper than 48.00 diopters;
3. Had history of ocular surgery within the last 3 months;
4. Had active ocular infection or inflammation;
5. Had an exceptionally small palpebral aperture size, short fornices, lid abnormality, or other anatomical obstacle resulting in inability to insert the LipiFlow activator.

Before each appointment, the patients were instructed to discontinue artificial-tear eye drops and contact lens use 12 hours before their visit and to discontinue use of ocular ointments 24 hours before their visit. All clinical tests performed at baseline visits were repeated at the follow-up visit and were completed in an order from least to most invasive, as shown below.

Questionnaires

Two questionnaires were used—Standard Patient Evaluation of Eye Dryness (SPEED) and a custom survey designed by the Ocular Surface Imaging Clinic. At every visit, patients filled out the SPEED questionnaire, and a higher score was indicative of more dry eye symptoms.[14] An additional survey was administered to enable patients to describe their experience after treatment including the degree of symptom reduction (if any), the length of time after treatment that symptom reduction began, and how long the improvement persisted.

Vision Assessment

Monocular visual acuity was assessed using the M&S Smart System computerized vision chart (M&S Technologies Inc, Niles, IL). Patients wore their habitual distance spectacle correction if required; otherwise, acuity was measured unaided.

Lipid Layer Thickness and Blink Assessment

The LipiView Interferometer (TearScience, Inc) was used to capture a 20-second video per eye of the patient's blinking pattern. The software contains an algorithm that converts interferometric color units into nanometers of lipid layer thickness (LLT) in addition to calculating the number of partial blinks and total blinks (the remainder being full blinks).[15,16]

Corneal Topography

The Keratograph 5M (Oculus, Wetzlar, Germany) was used to acquire corneal topography to ensure that the cornea was not too steep to permit full vaulting of the cornea by the protective scleral shell of the LipiFlow device.

Noninvasive Tear Breakup Time

Noninvasive tear breakup time (NITBUT) was measured using the E300 Corneal Topographer (Medmont, Nunawading, Australia). The concentric circular mires reflected on the tear film were observed for the first sign of disruption. The measurement was performed using a stopwatch and was repeated three times for each eye.

Sodium Fluorescein Dye—Invasive Tear Breakup Time, Corneal Staining

Slit lamp biomicroscopy was used to evaluate the condition of the eyelids and ocular surface, as well as to measure palpebral aperture size. After the observation with white light of ocular adnexa and surface, invasive tear breakup time was measured by instilling a small amount of dye from Bio Glo sterile sodium fluorescein strips (Hub Pharmaceuticals LLC, Rancho Cucamonga, CA) wetted with Unisol 4 preservative-free saline solution (Alcon, Fort Worth, TX). The slit lamp with cobalt blue illumination and a Wratten filter were used to observe the first dark spot of the tear film. This measurement was repeated using a stopwatch three times for each eye. Subsequently, corneal staining was evaluated and graded using the Corneal and Contact Lens Research Unit standard scale,[17] which divides the cornea into five sections—superior, inferior, nasal, temporal, and central. If no staining was present, the section was given a score of 0. However, if staining was present, the type, extent, and depth of staining were each scored on a scale of 1 to 4. The eyelid margins were then dabbed with a dry sterile cotton swab to remove excess fluorescein dye before MG expressibility testing.

MG Expressibility

The Meibomian Gland Evaluator (TearScience, Inc) is a handheld device that enables depression of the outer eyelid margins with a controlled force of 1.25 g/mm^2, similar to that of a normal blink.[18,19] The device was held at a 45-degree angle against the eyelid margin for 10 to 15 seconds. Five glands were evaluated in each region of the eyelid—temporal, central, and nasal. For each gland showing secretion, meibum quality was scored on a scale of 0 to 3 corresponding to no secretion (grade 0), inspissated

secretion (grade 1), cloudy secretion (grade 2), or clear secretion (grade 3). The regional scores (0 to 15) and total scores (0 to 45) were calculated.[10,11] This procedure was repeated for the upper and lower eyelids of each eye. This test was performed before instillation of lissamine green (LG) dye because the LG dye can significantly obscure visibility of the meibum secretions.

LG Dye—Conjunctival Staining, Line of Marx, Lid Wiper Epitheliopathy

Preservative-free LG dye (Leiter's Compounding Pharmacy, San Jose, CA) was instilled in each eye and used to assess conjunctival staining using the Sjögren's International Collaborative Clinical Alliance classification criteria.[20] The conjunctiva was divided into four sections—superior, inferior, nasal, and temporal—and viewed with slit lamp biomicroscopy. The number of stained punctate dots was counted and scored as 0 to 9 dots (grade 0), 10 to 32 dots (grade 1), 33 to 100 dots (grade 2), or greater than 100 dots (grade 3). Staining over pingueculae or pterygia was not counted toward the total number of dots. Thereafter, the location of the line of Marx (LOM) was assessed on both the upper and lower eyelids. The location of the LOM was described in relation to the MGs as completely posterior to the glands (grade 0), parts touching the glands (grade 1), running along the glands (grade 2), or completely anterior to the glands (grade 3).[21] A LOM that is closer to the eyelid margin side has been shown to correlate with MGD but may also be associated with age.[9,21–23] Five minutes after the first LG drops were instilled, a second drop was instilled in each eye. One minute after instillation of the second LG drops, the upper eyelids were everted to evaluate presence and degree of lid wiper epitheliopathy. The horizontal length and sagittal width of the staining area were measured, and each was given a score according to the grading scale developed by Korb et al.[24] The length of staining was described as less than 2 mm (grade 0), 2 to 4 mm (grade 1), 5 to 9 mm (grade 2), or greater than or equal to 10 mm (grade 3). The sagittal width of staining was described as less than 25% of the wiper (grade 0), 25 to 50% of the wiper (grade 1), 50 to 75% of the wiper (grade 2), or greater than or equal to 75% of the wiper (grade 3).

Meibography

The Keratograph 5M (Oculus) was used to perform infrared meibography, producing a high-contrast image of MGs. To image MGs, the upper and lower eyelids were everted. Because of the size and positioning of the instrument, a single-handed technique to evert the lid was useful in obtaining the meibography images (see Supplemental Digital Content 1—a video that demonstrates a single-handed upper lid eversion technique, available at http://links.lww.com/OPX/A216). A meiboscore was given for each eyelid corresponding to the percentage of MGs affected by atrophy. The overall percentage of abnormalities of each lid was described as 0% (grade 0), less than 33% (grade 1), 33 to 67% (grade 2), or greater than 67% (grade 3).[25]

Eyelid Margin Debridement

A stainless steel spud was used to debride the lid margins to remove debris and blockages from the MG orifices (see Supplemental Digital Content 2—a video that demonstrates this method of eyelid margin debridement with a stainless steel spud, available at http://links.lww.com/OPX/A217).[26]

LipiFlow Thermal Pulsation System

Eligible candidates with no contraindications were cleared to proceed with LipiFlow treatment. The procedure lasted 12 minutes and both eyes were treated simultaneously. After treatment was completed, vision was assessed and patients were given written instructions to perform maintenance home therapy, which included warm compresses, digital massage of the eyelid margin, eyelid scrubs, and use of preservative-free artificial tears if needed, until their follow-up evaluation.

Data Analysis

Differences in dry eye symptoms and signs between baseline and follow-up visits were tested using the paired t test for continuous variables and the Wilcoxon signed rank test for ordinal variables. Univariate linear models were used to assess the significance of the associations between continuous outcomes and continuous explanatory variables, analysis of variance was used for continuous outcomes and a single categorical covariate (including binary variables), and the χ^2 test was used for count data and categorical variables. The Wilcoxon signed rank test was applied for testing associations between ordinal outcomes and a single binary covariate such as sex, and the Kruskal-Wallis test was applied for testing associations between ordinal outcomes and single multilevel (>2) categorical covariates. Multivariable regression models were constructed to estimate the effects of LipiFlow treatment on SPEED score. Models were adjusted by sex, age, and baseline SPEED score. The continuous independent variables baseline SPEED score, LLT, NITBUT, and age were centralized. Centralization refers to subtracting the variable's mean from each individual data value. Centralization of independent variables is sometimes recommended so that the intercept of the model can be interpreted as the expected value of the outcome when the independent variables are set to their means, that is, the centralized variables set to 0.

RESULTS

Descriptive Statistics

Data were analyzed from a total of 32 patients, with a mean (SD) age of 54.4 (15.0) years and a mean (SD) palpebral aperture size of 9.7 (1.4) mm. These patients completed a baseline visit and LipiFlow treatment, followed by a posttreatment visit that was, on average, 52 days (range, 21 to 84 days) after treatment. Of these patients, 21 were female (65.6%) and 11 were male (34.4%); 7 were Asian (21.9%) and 25 were non-Asian (78.1%). When patients were asked whether they felt their symptoms were improved, stable, or worse after a single LipiFlow treatment, 67% of patients reported improvements in their subjective symptoms, 5% reported a worsening of symptoms, and the remaining 28% of patients did not notice a difference.

SPEED Scores, Ocular Surface Conditions, and Their Interrelationships before and after LipiFlow Treatment

Clinical outcomes relating to dry eye symptoms and ocular surface evaluation before and after treatment are summarized in Table 1. The change in SPEED scores between visits was marginally associated with sex (p = 0.076), very weakly associated with age (p = 0.127), and not associated with race. Between-visit changes in MG expressibility score, number of total blinks, number of complete blinks, and corneal and conjunctival staining scores were not significantly associated with age, ethnicity, or sex. Male patients had, on average, 11.12 nm thinner LLT after treatment, whereas no change in LLT was observed for female subjects. Additionally, male subjects had, on average, 1.4 seconds longer NITBUT after treatment, compared with a difference of 0.4 seconds for female subjects.

There were a significantly greater number of glands associated with no expressibility (grade 0), than with presence of secretion (grades 1 to 3) at both visits ($p < 0.001$), indicating that the majority of MGs observed in this cohort were of the nonfunctional type. The numbers of MGs with grade 0 expressibility were not significantly different among the nasal, central, and temporal regions ($p > 0.05$). Fig. 1 summarizes the overall percentage patterns of MG expressibility grades in the three regions for the two visits. During the posttreatment visit, the number of nonfunctional glands (grade 0) decreased about 12, 15, and 11% in the central, nasal, and temporal regions, respectively. Number of glands with grades of 0 and 3 had significant changes after LipiFlow treatment ($p < 0.001$).

Figs. 2 and 3 depict the regional average staining scores of both eyes in cornea and conjunctiva, respectively. There was no statistically significant difference in the corneal staining scores between visits in any region. However, there was a significant decrease of 0.3 in nasal conjunctival staining score after treatment (p = 0.02). Scores in the other three regions were not significantly different between visits.

Baseline Patient and Ocular Factors Affecting Posttreatment SPEED

The goal of this model is to identify baseline ocular characteristics that are associated with changes in SPEED scores after treatment. The best-fitting model ($R^2 = 0.68$; overall model $p < 0.001$) is presented in Table 2. The degree of reduction of dry eye symptoms after treatment was associated with a higher baseline level of symptoms ($p < 0.001$), a higher number of secretory grade 0 MGs in the lower eyelids (p = 0.015), and higher grade of inferior conjunctival staining (p = 0.019) before treatment. In contrast, SPEED score changes were only weakly associated with baseline LLT (p = 0.073) and number of partial blinks (p = 0.112). There was a significant effect of sex on posttreatment SPEED score (p = 0.006) and a significant interaction between LLT and sex (p = 0.010).

In terms of the main effect sizes estimated by this model, if we compare female to male subjects, holding all other model explanatory variables to their average values, female subjects may expect a reduction in SPEED score after treatment (i.e., reduced symptoms) of about 1 unit, whereas male subjects may expect a reduction of about 5 units. Each additional MG of grade 0 found in the lower lid at baseline was associated with a decrease in SPEED score of 0.6 units after treatment, while holding other baseline variables constant. Finally, the largest impact on the posttreatment SPEED score among all baseline variables was the presence of inferior conjunctival staining. Patients were estimated to have a posttreatment SPEED score decreased by about 4 units for each grade unit higher of baseline inferior conjunctival staining, holding all other baseline variables constant.

DISCUSSION

Our analysis evaluated both objective and subjective findings in patients with MGD after a single LipiFlow treatment in a clinical setting. Unlike previous studies, our primary objective was to understand which patient and ocular characteristics at the baseline

TABLE 1.

Clinical test outcomes at baseline (visit 1) and posttreatment (visit 2) visits

	Visit 1		Visit 2				Paired test
Different outcomes	Mean	SD	Mean	SD	Mean difference	95% CI of mean difference	p
Speed score	15.7	5.5	12.9	5.7	−3.0	−4.4 to −1.2	**<0.001**
LLT, nm	66.2	22.9	61.5	20.5	−4.7	−9.9 to 0.50	0.073
NITBUT, s	6.1	3.2	7.6	2.6	1.5	0.6 to 2.3	**<0.001**
ITBUT, s	4.3	2.2	5.0	3.8	0.7	−0.2 to 1.7	0.121
MG expressibility score	17.3	12.9	29.0	12.6	7.8	−16.6 to −7.0	**<0.001**
Total blink	8.4	4.0	8.3	4.8	−0.1	−1.2 to 1.0	0.557
Complete blinks	6.1	4.9	5.5	5.5	−0.2	−1.6 to 1.2	0.548
Corneal staining	1.8	3.8	2.8	6.6	−0.2	—*	0.382
Conjunctival staining	1.4	2.1	1.4	2.0	−0.1	—*	0.569
LWE length	0.7	1.1	0.6	1.0	−0.2	−0.5 to 0.0	0.605
LWE width	0.6	1.0	0.5	0.9	−0.1	−0.2 to 0.0	0.925

Statistically significant values are in boldface.

*The Wilcoxon signed rank test was used to compare the median difference in ordinal variables between visits; thus, 95% CIs are not suitable here.

CI, confidence interval; ITBUT, invasive tear breakup time; LWE, lid wiper epitheliopathy.

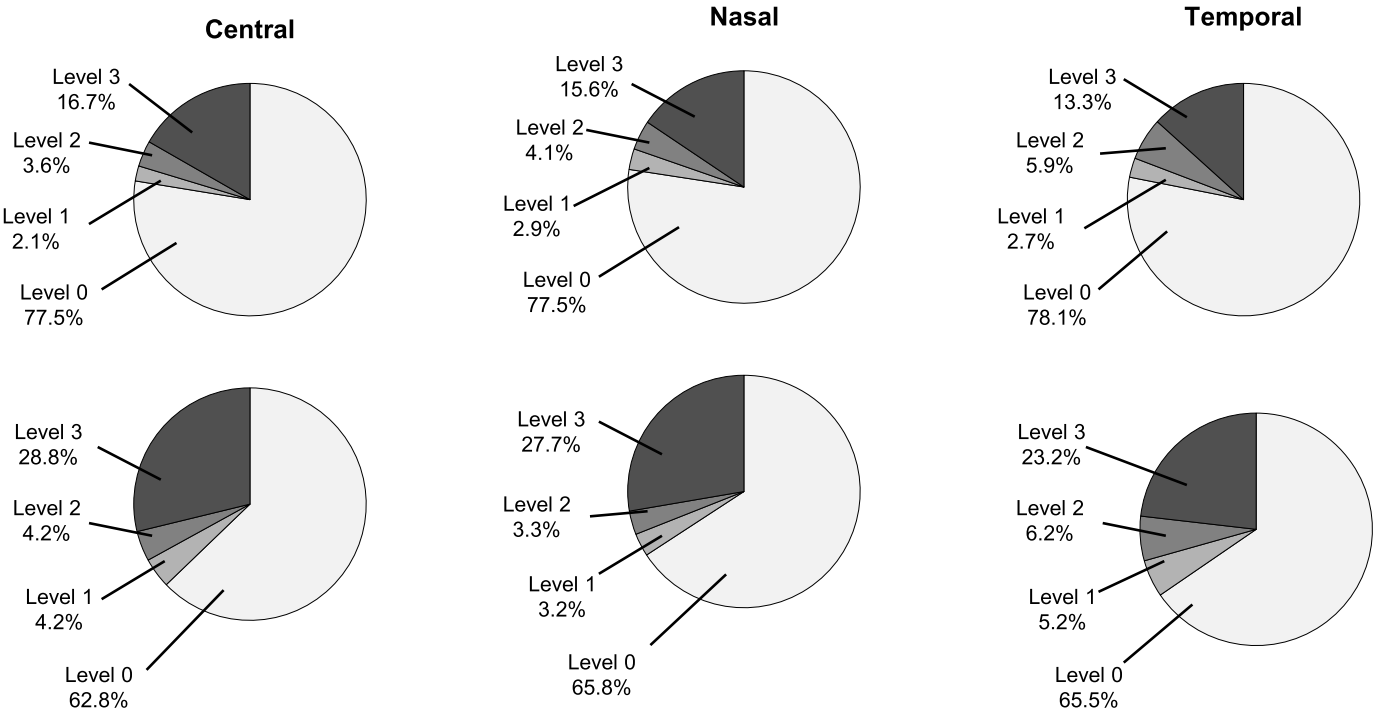

FIGURE 1.

Pattern distribution of the percentage of MGs with various levels of expressibility in the central, nasal, and temporal regions of the eyelids, before (top row) and after treatment (bottom row).

visit before a single treatment correlated with a successful outcome, not to determine whether LipiFlow is superior to traditional therapy. Every patient who provided data for analysis received a comprehensive ocular surface evaluation before and after treatment. Of all the clinical variables measured, a higher baseline inferior conjunctival staining and a greater number of unexpressible MGs at the lower eyelids were most significantly associated with a decrease of about 4 to 5 units in posttreatment SPEED score or a reduction in dry eye symptoms. The results from the model (Table 2) also suggest that baseline SPEED score and tear LLT may play a factor; however, their impact on the posttreatment SPEED score may not be clinically significant.

Perhaps the most intuitive of our findings is the association between successful outcome and the number of lower lid MGs with a score of "0" at baseline, indicating no secretion during MG expressibility. Korb and Greiner also identified reduced gland expression of lower lids at baseline, and that these subjects had greater potential for an increased net number of unblocked glands.[4,9,10] They speculated that higher yield of liquid secretion after treatment resulted in improved tear film stability. Our data

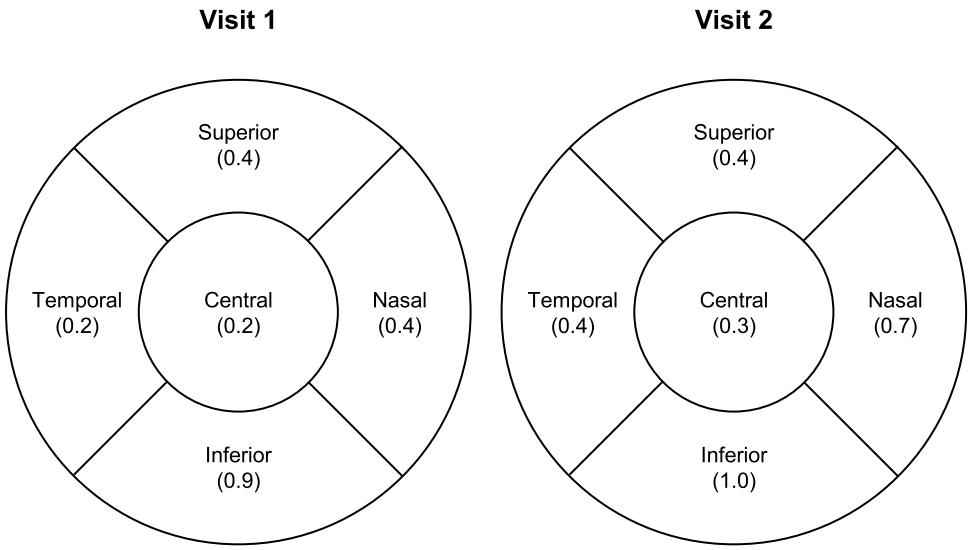

FIGURE 2.

Regional scores of corneal staining before (visit 1) and after (visit 2) treatment.

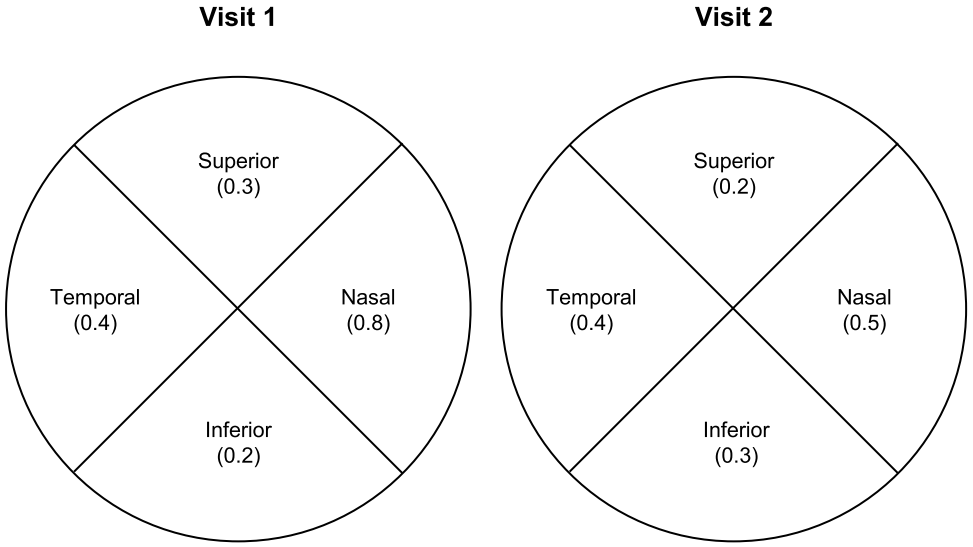

FIGURE 3.
Regional scores of conjunctival staining before (visit 1) and after (visit 2) treatment.

do not suggest a direct relationship between the number of unexpressible glands, tear-lipid thickness, and tear film stability but do support the idea that the greater change in number of open glands after treatment is associated with some improvement in dry eye symptoms.

Lissamine green ophthalmic dye is known to stain dead or devitalized cells and can reveal ocular surface disease, as intact conjunctival epithelium offers a barrier to the entry of vital dyes.[27] Conjunctival staining has been identified as an appropriate test for diagnosing MGD[28] but has not been identified as an important characteristic to consider when evaluating potential LipiFlow candidates. Finis et al.[13] evaluated conjunctival staining in their 6-month study and found no significant change from baseline to follow-up; however, only the nasal and temporal regions were scored. Based on our findings, LG staining in the inferior region of the conjunctiva at baseline was significantly associated with a decreased posttreatment SPEED score and thus suggests LG staining can be a useful tool to incorporate into the ocular surface evaluation before performing LipiFlow.

The most notable but surprising influential factor is sex. In our cohort, male patients had a much higher chance of being satisfied with the treatment outcome. Of particular interest is that the effect of LLT on the change in SPEED score is also greatly influenced by sex. Our data suggest that female patients had LLT that remained relatively the same after treatment whereas male patients had significantly decreased LLT that was associated with a decrease in SPEED score. Additionally, our male patients had more improvement in tear film stability than female patients after treatment. The fact that LLT decreased after treatment suggests that male patients with MGD in our cohort tended to have a hypersecretory disorder and had significant symptomatic improvement after LipiFlow treatment, suggesting that evacuation of the MG ducts assisted in the normalization of the tear-lipid layer, which in turn contributed to a more stable tear film.

Overall, our data yielded 67% of patients who reported subjective symptomatic improvement on the follow-up questionnaire. Of the remaining patients, 28% reported their symptoms were stable, whereas 5% reported their symptoms were worse. Of the patients whose symptoms worsened, these symptoms were often reported as transient and a result of either soreness attributed to an unusually short fornix or small palpebral aperture size compared with the activator scleral shell, or possible residual

TABLE 2.
Association of changes of SPEED score with baseline clinical conditions

Baseline variables	Estimated effects	SE	95% CI	p
Intercept	6.1	1.7	2.6 to 9.6	**<0.001**
SPEED (centralized)	−0.5	0.2	−0.8 to −0.2	**0.001**
LLT (centralized)	0.1	0.1	−0.0 to 0.2	0.068
NITBUT (centralized)	0.4	0.3	−0.2 to 1.0	0.217
Number of MGs with grade 0 in lower eyelids	−0.6	0.3	−1.2 to −0.1	**0.015**
Inferior conjunctival staining score	−4.1	1.7	−7.5 to −0.7	**0.019**
Partial blinks	0.5	0.3	−0.1 to 1.1	0.112
Sex	−5.14	1.8	−8.7 to −1.6	**0.006**
Age (centralized)	0.6	0.6	−0.1 to 0.2	0.338
LLT × sex	−0.2	0.1	−0.4 to −0.0	**0.010**

Statistically significant values are in boldface (overall model: $R^2 = 0.68$; adjusted $R^2 = 0.59$; $p < 0.001$).
CI, confidence interval.

inflammatory materials in the meibum secretions remaining on the ocular surface after obstructed glands were evacuated in a patient with permanent punctal plugs. It may be prudent to advise patients with punctal plugs of the possibility of symptoms temporarily worsening until the MGs begin to produce healthy meibum and the tear film normalizes. It may also be wise to remove punctal plugs on patients with MGD who do not have true aqueous insufficiency to prevent unhealthy meibum from lingering on the ocular surface. In our clinic, we observed that some patients complained of bulbar redness after treatment or home therapy treatment. For symptomatic patients after treatment, we may either prescribe a short course of antibiotics + anti-inflammatory combination topical ophthalmic medications to help alleviate symptoms or prescribe oral doxycycline (100 mg qd or 50 mg bid) if the quality of meibum persistently appears turbid.

Because our primary aim was not to determine the efficacy and effectiveness of LipiFlow treatment but to understand how to select patients for this treatment based on their baseline characteristics to improve their chances of a successful outcome, the drawbacks from having an open-label procedure without a control group were minimized. With that being said, our report is not without limitations. It is nearly impossible to avoid a possible ''placebo effect'' in the subjective outcomes owing to having a novel treatment. Additionally, it is difficult to assess the impact of increased patient awareness of their own conditions on the treatment outcome. Although every patient was given specific instructions on how to perform maintenance home therapy (warm compresses, digital eyelid massage, and eyelid hygiene were recommended twice daily), the compliance varied among subjects during the period between the initial and follow-up visit. Nevertheless, this exploratory analysis provided additional information to clinicians on patient selection for LipiFlow treatment. Further investigation with a larger sample size will continue to shed more light on the efficacy and effectiveness of this relatively new and expensive intervention for MGD.

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Meng C. Lin
School of Optometry
University of California, Berkeley
525 Minor Hall
Berkeley, CA 94720-2020
e-mail: mlin@berkeley.edu