Six-Month Effects of a Thermodynamic Treatment for MGD and Implications of Meibomian Gland Atrophy

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Purpose: The aim of this study was to evaluate the 6-month effect of a single automated thermodynamic treatment (LipiFlow) and implications of meibomian gland atrophy on treatment efficacy 6 months after application.

Methods: We analyzed the data of 26 subjects with meibomian gland dysfunction before and 6 months after treatment. Investigated parameters included subjective symptoms, lipid layer thickness, meibomian gland assessment, tear osmolarity, corneal and conjunctival staining, lid margin parallel conjunctival folds, Schirmer test values, bulbar redness, tear meniscus height, meibomian gland atrophy, and noninvasive tear break-up time.

Results: Subjective symptoms (mean Ocular Surface Disease Index, 42 ± 19 to 33 ± 21; \(P = 0.004\), mean Standard Patient Evaluation of Eye Dryness 16 ± 7 to 12 ± 7; \(P = 0.0001\)), lipid layer thickness (44.0 ± 15.6 to 51.3 ± 20.4; \(P = 0.014\)), number of expressible glands (2.9 ± 1.6 to 6.4 ± 4.6; \(P < 0.0001\)), lid margin parallel conjunctival folds (2.3 ± 1.0 to 2.0 ± 0.9; \(P = 0.04\)), and bulbar redness (1.4 ± 0.5 to 1.2 ± 0.5; \(P = 0.0001\)) were all improved 6 months after treatment. Symptomatic improvement was higher in patients with less severe meibomian gland atrophy compared with patients with more dropout at treatment. There was no change of meibomian gland atrophy 6 months after treatment.

Conclusions: In summary, the results showed that a single thermodynamic treatment is effective in the treatment of meibomian gland dysfunction and that the effects last for at least 6 months. We suggest performing meibography in every patient before treatment for better prediction of therapeutic effects.

Key Words: meibomian gland dysfunction, dry eye, LipiFlow

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Meibomian gland dysfunction (MGD) has recently gained increased attention as a major pathogenic factor for the development of dry eye; and therefore, several different therapeutic options, such as lipid containing tear substitutes, topical antiinflammatory drugs, or systemic use of tetracycline derivates have been developed in the past to improve this condition.

MGD is mainly caused by obstruction of the meibomian glands, which is due to increased keratinization of the ducal epithelium and increased viscosity of the meibum.\(^1\)–\(^9\) Lid margin hygiene still remains the basic therapy for MGD, which consists of eyelid warming and subsequent massage. In patients with MGD, the melting point of the meibum rises and its viscosity increases.\(^3\)–\(^4\) Warming of the eyelids is capable of reliquifying the meibomian lipids, thereby facilitating their delivery to the ocular surface by subsequent massage using cotton swab or fingertip pressure. Although manual lid margin hygiene can be a successful therapeutic approach for MGD, disadvantages include poor standardization and a potentially high number of noncompliant patients.

Recently, a new automated thermodynamic treatment device for patients with MGD was developed, the LipiFlow system (TearScience Inc., Morrisville, NC). This consists of a single 12-minute in-office treatment first described by Korb and Blackie\(^10\) in a case report. After several case series indicating efficacy,\(^11\)–\(^13\) a prospective, randomized multicenter study found superiority of a single thermodynamic treatment over twice-daily lid warming over 4 weeks.\(^14\) Our own group was able to demonstrate in a prospective randomized, observer-masked study with a crossover design that a single 12-minute in-office LipiFlow treatment is as least effective as a combination of lid warming, massage, and cleaning performed twice daily at home over 3 months.\(^15\)

Although these studies indicate the efficacy of a single automated thermodynamic lid margin treatment, this treatment is also substantially more cost-intensive than the historic manual approach. A nonresponder rate of approximately 20% (regarding the reduction of subjective symptoms) was found in our own prospective trial and in the study by Lane et al.\(^14\) To reduce financial burden to individuals or healthcare providers, it is important to identify potential nonresponders before treatment. To test our hypothesis that efficacy of this new treatment depends on the extent of preexisting meibomian gland atrophy, we analyzed this parameter and the 6-month efficacy data of the continuously followed cohort of our initial randomized trial.
MATERIALS AND METHODS

The study followed the tenets of the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from subjects after the nature and possible consequences of the study had been explained to them. The study was approved by the ethics committee of the Heinrich-Heine-University Düsseldorf.

We analyzed the 6-month data of 26 patients who participated in our initial prospective randomized trial. All patients were analyzed who received the treatment and completed a follow-up of 6 months. Seventeen of the 26 patients received the treatment directly after randomization. Nine of the 26 patients received the treatment 3 months after randomization as part of a crossover design after an initial instruction to perform a combination of lid warming and manual massage twice daily at home for 3 months.

We included patients at least 18 years of age, who gave informed consent to participate in the study and who had treatment requiring MGD, defined as a Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score of ≥8, lipid layer thickness (LLT) of ≥61 nm, and expressible meibomian glands of ≥4 (for details see below).

We excluded patients with systemic medication with tetracycline derivatives, antihistamines, isotretinoin, or nutritional supplements for MGD within the last 3 months before baseline examination, topical cyclosporine-A or steroid use within 1 month before baseline examination, ocular surgery or trauma within 3 months before baseline examination, or any eyelid abnormalities or systemic diseases resulting in dry eye.

Participants were instructed to continue the use of ocular lubricants as before inclusion into the trial. All subjects received a single thermodynamic treatment, as described in detail by Lane et al. In brief, a topical anesthetic (oxybuprocaine hydrochloride 4.0 mg/mL) was applied before treatment, followed by bilateral application of a 2-part single-use activator. The inner portion of the activator applies a constant temperature of 42.5°C to the tarsal conjunctiva of the upper and lower eyelids. The outer portion of the activator covers the skin of the upper and lower lids and applies a pressure of 3 psi for 2 minutes, followed by 2 minutes of steadily increasing pressure from 0 to 3 psi and 2 minutes of alternating pressure (0–5.5 psi). This cycle is repeated once again so that both eyelids simultaneous receive warming and massaging for 12 minutes.

At all study visits, subjective symptoms [Ocular Surface Disease Index (OSDI) and SPEED], LLT, tear film osmolality, tear break-up time (TBUT), tear meniscus height, bulbar redness (R-score), meibography, ocular surface staining, lid margin parallel conjunctival folds (LIPCOFs), and number of expressible meibomian glands were evaluated in the sequence given below.

First, the patients were asked to complete 2 symptom questionnaires—OSDI and SPEED. OSDI scores range from 0 (no symptoms) to 100 (severe symptoms). SPEED scores range from 0 (no symptoms) to 28 (severe symptoms). LLT was measured using the LipiView interferometer (TearScience Inc, Morrisville, NC). This method has been described in detail by Blackie et al. In brief, a video of the patient’s tear film interference patterns is recorded. These patterns are then analyzed, and a value of interferometric color units (ICUs) is created (1 ICU reflects a lipid layer approximately 1 nm thick).

For detection of tear film osmolality, the TearLab Osmolarity System (TearLab Corporation, San Diego, CA) was used. Samples were taken without local anesthesia from the lateral tear meniscus of both eyes. The system was calibrated according to the manufacturer’s instructions.

TBUT, tear meniscus height, bulbar redness, and meiboscore were measured using the Oculos Keratograph 5M corneal topographer (Oculus, Wetzlar, Germany). The TBUT was detected automatically and noninvasively. We used the time point of the first break-up for the analysis. Tear meniscus height was detected in the middle of the lower eyelid under the center of the pupil. The measuring points were determined by the investigator, and afterward they were analyzed automatically by the topographer, which also automatically measured bulbar redness as a value between 0 (white eye, no conjunctival injection) and 4 (maximum conjunctival hyperemia). Meibography was performed and analyzed according to Arita et al. First the meibomian glands of the upper than the lower eyelid were visualized and graded. No atrophy corresponds to 0 point, less than one third to 1 point, more than one third to 2 points, and more than two thirds to 3 points. The values for the upper and lower eyelid were then added, resulting in a total score of 0 to 6. Figure 1 shows a patient with no meibomian gland atrophy (meiboscore 0) and a patient with severe meibomian gland atrophy (meiboscore 6). All meibography images were analyzed by 2 independent investigators. If the gradings of the 2 investigators did not match, the images were reevaluated by them together and the score was discussed until a unanimous decision between both was achieved. This score was used for the final analysis. For the detection of changes in the degree of meibomian gland atrophy, we compared the pretreatment and posttreatment images displayed on one screen.

Ocular surface staining was measured 2 minutes after instillation of a single drop of fluorescein (1.5 mg fluorescein/mL). Staining was evaluated using a slit-lamp equipped with a cobalt blue exciter filter and then graded according to the Oxford grading system. The cornea and 2 conjunctival zones (nasal and temporal) were graded according to a chart-based scale using scores of 0 to 5 per zone, resulting in a total range of 0 to 15.

LIPCOFs were graded as described by Hoeh et al in the temporal third of the eyelid. Lack of a permanent existing LIPCOF was graded as 0; a small fold, that is, 1 lower than the normal tear meniscus, was graded as 1; a significant fold up to the height of the normal tear meniscus was graded as 2; large multiple wrinkled folds exceeding the height of the normal tear meniscus were graded as 3; and a large fold that extended over the inner lid margin as 4 (Fig. 2).

The number of expressible meibomian glands was quantified using the Meibomian Gland Evaluator (TearScience). With this handheld instrument, a defined pressure is applied to the lateral, middle, and medial third of the lower eyelid, and the number of expressible glands is counted, as described by Korb and Blackie. In addition to the number of expressible glands, we also evaluated the type of secretion.
A clear fluid was graded as 0, a cloudy fluid was graded as 1, a cloudy fluid with cellular debris was graded as 2, and a toothpaste-like secretion was graded as 3.19

The Schirmer test was performed without anesthesia, with the eyelids closed for 5 minutes. Mark Blu Schirmer Tear Test strips (Optitech Eyecare, Allahabad, India) were placed between the lateral and middle thirds of the lower eyelid.

Statistical analysis was performed using Microsoft Excel 2010 and GraphPad Prism version 6. To analyze the changes between the different time points, paired t tests were used. To analyze the differences between different subgroups, heteroscedastic t tests were used. A P value, 0.05 was considered statistically significant.

RESULTS

A total of 26 subjects (52 eyes, 50 ± 22 years, 19 women, 7 men) completed the follow-up of 6 months. The meiboscore in our study collective was not normally distributed (Fig. 3). Both raters evaluated the meibography images with a high concordance (r = 0.94, P < 0.001).

We found a significant reduction of subjective symptoms from baseline 42 ± 19 OSDI score to 33 ± 21 OSDI score 6 months after treatment (P < 0.005). Also, SPEED values were significantly reduced from 16 ± 7 at baseline to 12 ± 7 six months after treatment (P < 0.001) (Fig. 4). Overall, 19 of the 26 patients (73.0%) showed a reduction of the OSDI score and 22 of the 26 patients (84.6%) showed a reduction of the SPEED score.

In addition, a single thermodynamic treatment increased the LLT from 44.0 ± 15.6 ICUs to 51.3 ± 20.4 ICUs; P < 0.05) (Fig. 4) and the number of expressible meibomian glands from 2.9 ± 1.6 to 6.4 ± 4.6 (P < 0.0001). This was also true if the individual areas (nasal, middle, and lateral third) of the lower eyelid were assessed. The number of expressible meibomian glands in the nasal third of the lower eyelid increased from 1.0 ± 0.9 to 2.1 ± 1.8 (P < 0.0001), in the middle third of the lower eyelid from 0.9 ± 0.9 to 2.3 ± 1.7 (P < 0.0001), and in the lateral third of the lower eyelid from 1.0 ± 1.0 to 1.9 ± 1.7 (P < 0.005) (Fig. 4). There was no significant difference between the number of expressible glands of the individual thirds of the lower eyelid. In addition, a decrease of the secretion score from 0.9 ± 0.8 to 0.5 ± 0.9 (P < 0.05) was noted.

LIPCOFs decreased from 2.3 ± 1.0 before to 2.0 ± 0.9 six months after a single thermodynamic treatment (P < 0.05). Bulbar redness was reduced from 1.4 ± 0.5 to 1.2 ± 0.5 after treatment (P < 0.001) (Fig. 4). TBUT (9.5 ± 8.7 to 10.0 ± 6.7 seconds; P = 0.72), osmolarity (302 ± 10 to 299 ± 13 mOsm/L; P = 0.42), Schirmer test (14.0 ± 10.4 to 16.5 ± 11.0 mm/5 minutes; P = 0.13), tear meniscus height (0.4 ± 0.31 to 0.37 ± 0.23 mm; P = 0.32), and Oxford scale staining (2.0 ± 2.0 to 2.4 ± 2.3; P = 0.36) remained unchanged.

The comparison of pretreatment and posttreatment meibography images did not show any difference in the degree of meibomian gland atrophy. Patients with severe meibomian gland atrophy (drop out ≥2/3 of all glands = meiboscore 6) did show less improvement of subjective symptoms compared with patients with less drop out. However, there was no significant difference regarding reduction of the OSDI for the comparison of patients with a meiboscore

FIGURE 1. Comparison of a patient with severe meibomian gland atrophy (meiboscore 6) on the right side and a patient with almost no meibomian gland atrophy (meiboscore 0) on the left side.

FIGURE 2. LIPCOFs. Large, multiple wrinkled fold exceeding the height of the normal tear meniscus, which was graded as 3. Usually, the grading of LIPCOFs is performed without any vital stain. For this image, fluorescein (1.5 mg fluorescein/mL), a cobalt blue exciter filter, and a yellow observation filter were used for better visualization of the folds.
from 0 to 4 with patients with a meiboscore from 5 to 6 or for the comparison of patients with a meiboscore from 0 to 3 with patients with a meiboscore from 4 to 6 (Fig. 5). In addition, patients with severe meibomian gland atrophy (meiboscore 6) did show less improvement of expressible glands compared with patients with less drop out. Again, there was no significant difference regarding the increase in the number of expressible glands for the comparison of patients with a meiboscore from 0 to 4 with patients with a meiboscore from 5 to 6 and of patients with a meiboscore from 0 to 3 with patients with a meiboscore from 4 to 6 (Fig. 6). The same analysis was performed for all other investigated parameters and revealed no significant differences except for LLT. The LLT for patients with severe meibomian gland atrophy (meiboscore 6) was not significantly different compared with patients with a lower meiboscore from 0 to 5, but there was more significant improvement of LLT in patients with a meiboscore from 5 to 6 compared with patients with a meiboscore from 0 to 4 (15.8 ± 16.9 vs. 5.1 ± 22.0 ICUs; \( P = 0.043 \)) and for patients with a meiboscore from 4 to 6 compared with patients with a meiboscore from 0 to 3 (14.6 ± 16.0 vs. 4.9 ± 18.4 ICUs; \( P = 0.047 \)).

**DISCUSSION**

The results of this study revealed that a single 12-minute in-office thermodynamic treatment significantly reduced subjective symptoms and improved objective dry
eye parameters (expressible glands, secretion score, LLT, and LIPCOFs). Several studies reported the advantages of this new treatment, but, however, this is the first prospective trial that confirms positive treatment effects for 6 months including an improvement of LLT using a novel ocular surface interferometer (LipiView). Although, only a semiquantitative grading was used for analysis of LLT in previous studies, this new method is capable of an observer-independent quantification. LLT has been shown to correlate with other dry eye parameters. However, placebo effects of the treatment cannot be completely excluded because participants knew that they were receiving a new and potentially expensive treatment for MGD. Although a placebo effect cannot be ruled out, it has to be considered that it might be of limited duration. For a 12-minute treatment, it seems unlikely that after 6 months, there was still a strong placebo effect. Nevertheless, because there is no prospective, randomized, truly double-masked study comparing a manual versus an automated thermodynamic lid margin treatment, this should be addressed in future studies.

Another important finding of this study is the improvement of bulbar redness (R-score). This recently developed scoring system implemented in the Oculus Topographer 5M is again an observer-independent parameter. Although, to the best of our knowledge, no validation study of this tool has been published so far, conjunctival inflammation and hyperemia is known to be present in dry eye. Reduction of bulbar redness in our study could thus be interpreted as a sign of reduced inflammation and improved ocular surface conditions after treatment.

This study is also the first to report a small but significant improvement of LIPCOFs after a LipiFlow treatment, which has been shown to correlate well with dry eye symptoms. However, conclusions based on mild improvement from 2.3 to 2.0 on a 4-point scale should be regarded very carefully.

Although we detected a sustained improvement of subjective symptoms and several objective parameters over 6 months after a single thermodynamic treatment, we were unable to show any morphological changes of the meibomian glands with noncontact meibography. The increased number of expressible glands and LLT therefore indicates that this treatment was able to overcome obstruction and dysfunction of the remaining meibomian glands, whereas it was impossible to revitalize atrophic glands. This may explain why patients with a more early stage of MGD are more likely to benefit from this treatment and why patients with most extensive and severe meibomian gland atrophy did respond poorly. This is also in accordance with a case described by Korb and Blackie, who found an improvement of subjective symptoms and the number of expressible glands after a single thermodynamic treatment in a patient with partial meibomian gland atrophy. According to the results of this study, we suggest performing meibography in every patient before thermodynamic treatment modalities for better prediction of therapeutic effects. However, because some of the patients with minimal meibomian gland atrophy (meiboscore 1) were poor responders, other parameters, such as incomplete blinks, may have an influence on the treatment response. In addition, the period of 6 months may have been too short to detect changes in meibography. Regrowth of new glands and new ducts may take longer time.

In summary, this study shows that a single in-office thermodynamic treatment reduces subjective symptoms and objective dry eye parameters in patients with MGD over 6 months but has no effect on atrophy of meibomian glands as visualized by meibography. The treatment response is not linearly correlated with the degree of meibomian gland atrophy, but patients with very severe atrophy (meiboscore 6) should be regarded as potential nonresponders. Future studies should aim to identify confounding factors that may influence treatment results. Also, a prospective, randomized double-masked trial is needed to prove the efficacy of an automated and hence cost-intensive thermodynamic treatment such as LipiFlow.

REFERENCES


29. Korb DR, Blackie CA, McNally EN. Evidence suggesting that the keratinized portions of the upper and lower lid margins do not make complete contact during deliberate blinking. Cornea. 2013;32:491–495.