Comparison of an Automated Thermodynamic Treatment System (LipiFlow) and Warm Compresses for the Treatment of Moderate Severity of Meibomian Gland Dysfunction

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ABSTRACT

Objective: To compare the efficacies of a single thermodynamic treatment system (LipiFlow®) and warm compresses used for 3 months in patients with a moderate severity of meibomian gland dysfunction (MGD).

Methods: This prospective, randomized, controlled clinical study enrolled 28 patients (22 females, 6 males; mean age, 53.9 ± 14.8 years) diagnosed as having moderate MGD by plugging at the meibomian gland orifices between one-third and two-thirds of lid margins and at least one of the following: a Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score of 6-12; a lipid layer thickness (LLT) score of 40-70 Interferometric Color Units; upper eyelid meiboscore of 1-2; and 3-6 expressible meibomian glands (EMGs) in the lower eyelid. Both eyes of each patient were randomized into study and control eyes. Study eyes were treated with a single, 12-minute LipiFlow® system, while control eyes received 5-minute warm compresses twice daily for 3 months. The dry eye symptoms, the number of EMGs, and LLTs were evaluated.

Results: There were no significant differences in the dry eye symptoms, number of EMGs, and LLTs for both groups at baseline and at each follow-up. However, the total SPEED scores for the LipiFlow® group reduced significantly from baseline at each follow-up until 6 months. As to the warm compress group, the total SPEED scores reduced significantly from baseline at each follow-up until 3 months.

Conclusion: The single LipiFlow® treatment and twice-daily warm compresses relieved the dry eye symptoms of patients with a moderate severity of MGD compared with their baseline symptoms, despite no statistical differences in the dry eye symptoms, number of EMGs, and LLTs of both treatments.

Keywords: Meibomian gland dysfunction; warm compresses; automated thermodynamic treatment system; LipiFlow® (Siriraj Med J 2020; 72: 79-86)

INTRODUCTION

Meibomian gland dysfunction (MGD) is a chronic, diffuse, terminal duct obstruction of the Meibomian glands (MGs) involving qualitative or quantitative changes in glandular secretions.[1] It results in an alteration of the tear film and causes the majority of evaporative dry eyes, ranging from 38% to 68% of the population.[2] Patients with MGD experience eye irritation, a burning sensation, difficulty opening the eyelids, and blurred vision. The management of MGD includes the replacement of the MG

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secretion with topical oil emulsion formulations, the use of ocular ointments, the release of the MG obstruction, and the restoration of normal MG secretion. Current methods to relieve MG obstruction include eyelid margin cleansing, eyelid warming and eyelid massaging twice daily[3,4] and practitioner-administered manual expression.[5]

However, it is difficult to maintain warm compresses at a constant temperature between 32°C and 40°C (the reported melting temperature range of normal MG secretions) for 5 minutes.[6] Moreover, patients find that the twice-daily administration of an effective warm compress is both inconvenient and time-consuming, resulting in poor compliance. Although practitioner-administered manual expressions of MGs are more effective at releasing MG obstructions, their application is limited due to the associated pain. A new treatment modality, the LipiFlow® Thermal Pulsation System (TearScience Inc., Morrisville, NC, USA), may help to solve the limited success rate of warm compresses. This technology involves a single, 12-minute treatment that allows heat to be applied to the palpebral surfaces of the upper and lower eyelids directly over the MGs while simultaneously applying graded, pulsatile pressure to the cutaneous eyelid surfaces, thereby expressing the MGs during heating.[7-9] Many studies have shown that a single LipiFlow® treatment results in sustained improvement in both the signs and symptoms of MGD at 1 month,[10-12] 3 months,[9,13-15] 6 months,[16] 9 months[17] and 1 year post-treatment.[18-19] However, Finis and colleagues found that this single LipiFlow® treatment poorly benefited patients with severe MGD or MG atrophy.[16] Because of the high cost of this single LipiFlow® treatment, it is essential to identify potential non-responders or poor responders before treatment. To our knowledge, there has been no prospective, randomized, controlled clinical study of the efficacy of this treatment in patients with a moderate severity of MGD. Thus, this study evaluated the efficacy of this new treatment and compared it with the twice-daily application of warm compresses for patients with moderate MGD.

MATERIALS AND METHODS

This prospective, observer-masked, randomized, controlled clinical trial was conducted at Siriraj Hospital, Faculty of Medicine Siriraj Hospital, Mahidol University, Thailand, between January 2015 and June 2016. The study was approved by the Institutional Review Board and followed the tenets of the Declaration of Helsinki for research involving human subjects (Si 725/2014; Thai clinical trial registration number: TCTR 20170905001). Written, informed consent was obtained from all patients before enrollment. The inclusion criteria were patients at least 18 years of age who had a moderate severity of MG obstruction, defined in this study as follows: the presence of plugging at the MG orifices between one-third and two-thirds of total lid margin area and at least one of the following: (1) a Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire score of 6-12[15,20-21]; (2) a lipid layer thickness (LLT) score of 40-70 ICU (Interferometric Color Units), measured by using a LipiView® interferometer (TearScience Inc., Morrisville, NC, USA)[22]; (3) an upper eyelid meiboscore of 1-2, obtained by using a Meibography® (Oculus, Wetzlar, Germany), using the grading scales developed by Arita et al.[23]; and (4) 3-6 expressible MGs (EMGs) in the lower eyelid.[15,21] The exclusion criteria were patients with systemic diseases resulting in dry eyes (such as systemic lupus erythematosus, rheumatoid arthritis, and allergic diseases); patients who had eyelid abnormalities, previous ocular surgery, or trauma; and patients who used systemic medications affecting dry eyes (for instance, antihistamines, tetracycline derivatives, isotretinoin, and topical cyclosporine A) or steroids in the preceding month.

All patients completed the SPEED questionnaires by themselves. Then, the MGs of all patients were evaluated using a Meibography® and LLTs were measured using a LipiView® interferometer. Both the meiboscores and LLTs were measured by one examiner (P. Chonpimai). Complete ocular examinations of the anterior and posterior segments, including an assessment of the expression of the MGs of the lower eyelids of both eyes using a Meibomian Gland Evaluator (TearScience Inc., Morrisville, NC, USA), were performed by cornea specialists (W.B., P.P., S.C., and P.K. and two cornea fellows (P.N. and W.T.).

Dry eye symptoms were recorded as total SPEED scores, derived from the sum of the frequency and severity scores for all symptoms over a range from 0 to 28. A higher score represented more frequent and/or more severe symptoms.[20,24]

The number of EMGs was quantified, as described by Korb and Blackie.[21] The MGs of the lower eyelids were expressed by the Meibomian Gland Evaluator, being pressed with approximately 1.2 g/mm^2 of pressure along the distal end of the MGs at the nasal, central, and temporal parts of the lower eyelids. Each part consisted of 5 consecutive MG orifices, which meant that a total of 15 MGs were expressed. The number of EMGs was recorded.

The LLTs were ascertained by using a LipiView® interferometer, as described by Blackie et al.[22] The patients' tear film interference patterns were recorded and analyzed

as a value of interferometric color units (ICU; 1 ICU refers to approximately a 1-nm thickness of lipid layer).

The right and left eyes of each patient were randomized into a study eye and a contralateral control eye. The study eye was treated with a single, 12-minute, LipiFlow® Thermal Pulsation System, whereas the control eye was treated with a 5-minute warm compress twice daily for 3 months. The LipiFlow® treatment was utilized as described in detail by Lane et al.[11] Briefly, two drops of a topical anesthetic (0.5% tetracaine hydrochloride) were applied to the study eye prior to treatment. The LipiFlow® device applied heat (42.5°C) to the upper and lower inner eyelid surfaces directly over the MGs, while a pulsating pressure was simultaneously applied to the outer eyelids using an inflatable air bladder.[11] This device was capable of melting the MG contents without thermal injury, and of simultaneously evacuating the MGs of the upper and lower eyelids. The control eye was treated with warm compresses. The patients were instructed to soak a hand towel or washcloth in hot water, wring out the excess water, and then place the warm towel or cloth over the skin of the closed eyelids of the control eye, applying gentle pressure for 5 minutes.[6]

The study parameters were the dry eye symptoms determined by using the total SPEED scores and an assessment of the MG function, measured by the number of EMGs and the LLT scores. These three parameters were evaluated at baseline and at the follow-up times of 1 day, 1 week, 1month, 6 weeks, 3 months and 6 months.

Artificial tear eye drops (0.18% sodium hyaluronate) were prescribed for application into both eyes every 2 hours for all patients during the study.

Sample size

To calculate the sample size, a power analysis and the effect size using the data of Lane et al.,[11] which showed the improvements in the number of EMGs, were performed. On this basis, the minimum sample size was 20 patients per group. However, to ensure adequate reliability and to compensate for patient loss, 30 patients per group were enrolled.

Statistical analysis

Descriptive statistics were used to demonstrate the patients' baseline characteristics. The categorical data were described as numbers with percentages, while the continuous data were presented as mean with standard deviation (SD) or mean differences with the corresponding 95% confidence interval. The unpaired t-test was utilized to compare the continuous data of the LipiFlow® and control groups, whereas the paired t-test was used to compare the continuous data within the groups. All analyses were performed using PASW Statistics for Windows, version 18 (SPSS Inc., Chicago, IL, USA). All tests of significance were two tailed, and a p-value<0.05 was considered statistically significant.

RESULTS

A total of 33 patients were enrolled. However, only 28 completed the study because 3 patients were lost to follow-up after the baseline examination, and 2 patients did not return for the 6-month follow-up. Twenty-two patients were female (78.6%), and six were male (21.4%). The mean age was 53.9±14.8 years. There were no statistical differences in the meiboscores of the LipiFlow® and warm compress groups at baseline (p=0.745).

As to the total SPEED scores, there were no statistically significant differences between the LipiFlow® and the warm compress groups at baseline and at each follow-up (Table 1). However, in the case of the LipiFlow® group, there was a statistically significant, greater reduction in the total SPEED scores at each follow-up until 6 months, compared to the scores at baseline (Table 1). Similarly, the warm compress group showed a statistically significant, greater reduction in the total SPEED scores at the 1-week, 1-month, 6-week and 3-month follow-ups, compared to those at baseline (Table 1). However, after stopping the warm compresses at the 3-month follow-up, the total SPEED scores for the warm compress group were not changed significantly at the 6-month follow-up, compared to those at baseline (Table 1). In other words, the total SPEED scores for the warm compress group returned to near-baseline level at the 6-month follow-up after the application of the warm compresses ceased at the 3-month time point.

In a comparison of the number of EMGs of the two groups, the LipiFlow® group showed a greater increase in the number of EMGs than the warm compress group at every follow-up. Nevertheless, those greater increase were statistically significant on only two occasions: at the 1-day and the 3-month follow-ups (p=0.048 and p=0.049, respectively; Table 2).

Regarding the LLTs, there were no statistically significant differences in the LLTs of both groups at baseline and at each follow-up (Table 3). However, the warm compress group had a statistically significant greater reduction in the LLT scores at the 1-day and 1-week follow-ups, compared to those of baseline (p=0.004 and p=0.031, respectively; Table 3).

TABLE 1. Comparison of the dry eye symptoms (SPEED scores) for both groups and between baseline and at each follow-up for each group.

	SPEED scores (mean ± SD)		
	Warm compresses	**LipiFlow®**	**P-value[a]**
Baseline	9.2 ± 4.4	9.5 ± 4.5	0.781
Follow-up time			
1 day	7.4 ± 5.2	7.8 ± 4.2	0.531
Δ 1 day	-1.6 ± 4.4	-1.8 ± 2.9	
p-value[b]	0.062	0.003	
1 week	7.4 ± 4.7	7.1 ± 4.5	0.924
Δ 1 week	-2.1 ± 4.0	-2.7 ± 3.8	
p-value[b]	0.007	0.001	
1 month	6.3 ± 4.6	5.8 ± 4.1	0.731
Δ 4 weeks	-2.5 ± 4.1	-3.3 ± 3.6	
p-value[b]	0.006	<0.001	
6 weeks	6.7 ± 4.7	6.5 ± 4.2	0.777
Δ 6 weeks	-2.3 ± 5.2	-3.0 ± 4.5	
p-value[b]	0.035	0.003	
3 months	6.7 ± 4.4	6.7 ± 4.4	1.000
Δ 3 months	-2.7 ± 4.2	-2.7 ± 3.5	
p-value[b]	0.004	0.001	
6 months	7.9 ± 5.8	7.8 ± 5.3	0.954
Δ 6 months	-1.3 ± 5.1	-1.9 ± 4.7	
p-value[b]	0.238	0.034	

[a]comparison of SPEED scores for both groups, [b]comparison of SPEED scores between baseline and at each follow-up for each group, Δ = mean change in SPEED scores from baseline to each follow-up for each group

Adverse events

There were no serious, device-related, adverse events in the LipiFlow® group, and no adverse events in the warm compress group. The only device-related, adverse event was eye discomfort or pain, which occurred among patients with small eyes, narrow palpebral fissure, or deep-set eyes.

DISCUSSION

The present study showed that both the single, 12-minute, thermodynamic treatment system (LipiFlow®) and the twice-daily warm compresses were able to relieve the dry eye symptoms of patients with a moderate MGD compared to their baseline symptoms, despite there being no statistical differences in the dry eye symptoms for both treatments. In fact, the dry eye symptoms of the LipiFlow® group decreased faster at the first day post-treatment, and they continued to decrease to 6 months post-treatment. In contrast, the dry eye symptoms of the warm compress group began to reduce later, at the one-week follow-up, and sustained the reduction only while the participants applied the warm compresses twice daily for 3 months. When they stopped the warm compresses, their symptoms reappeared. Many studies[9-19] have reported that a single LipiFlow® treatment had a statistically significant greater reduction in dry eye symptoms than warm compresses at 1 month until 1 year post-treatment. In contrast to those findings, the

TABLE 2. Comparison of the number of expressible meibomian glands (EMGs) for both groups and between baseline and at each follow-up for each group.

	The number of EMGs (mean ± SD)		
	Warm compresses	LipiFlow®	P-value[a]
Baseline			
Follow-up time	2.5 ± 2.3	2.6 ± 2.8	0.885
1 day	2.0 ± 2.0	3.0 ± 2.0	0.048
Δ mean (95%CI)	-0.7 (-1.6, 0.2)	0.3 (-1.2, 1.7)	
p-value[b]	0.156	0.536	
1 week	2.5 ± 2.1	3.7 ± 3.3	0.153
Δ mean (95%CI)	-0.1 (-1.1, 1.0)	1.3 (-0.5, 3.0)	
p-value[b]	0.951	0.152	
1 month	2.6 ± 2.2	3.5 ± 3.1	0.471
Δ mean (95%CI)	0.1 (-1.1, 1.3)	0.7 (-0.8, 2.2)	
p-value[b]	0.847	0.352	
6 weeks	2.3 ± 2.4	2.4 ± 2.3	0.827
Δ mean (95%CI)	-0.4 (-1.7, 0.9)	-0.6 (-2.1, 1.0)	
p-value[b]	0.556	0.660	
3 months	2.3 ± 2.0	3.6 ± 2.2	0.049
Δ mean (95%CI)	-0.3 (-1.4, 0.8)	0.8 (-0.5, 2.0)	
p-value[b]	0.494	0.066	
6 months	2.7 ± 2.2	3.1 ± 2.1	0.369
Δ mean (95%CI)	0 (-1.2, 1.2)	0.3 (-1.1, 1.6)	
p-value[b]	0.862	0.557	

[a]comparison of the number of EMGs for both groups, [b]comparison of the number of EMGs between baseline and at each follow-up for each group, Δ mean (95%CI) = mean change in the number of EMGs from baseline to each follow-up for each group (95% confidence interval)

results of the present study were the same as those of other reports[16,25] that did not demonstrate a statistically significant difference in the dry eye symptoms between the single LipiFlow® treatment and the twice-daily warm compresses, nor in the number of EMGs and LLTs, despite a tendency to improve those three parameters in the patients receiving the LipiFlow® treatment. The current study could not demonstrate a statistical difference in the dry eye symptoms of both treatments, and the mean SPEED scores found in this study were less than those reported by other researches.[8-12,17-18] This may be due to the small sample size and the enrollment of only patients with a moderate MGD.

Concerning the MG function, the number of EMGs and LLT scores were evaluated. The number of EMGs was derived from the number of MGs in which the obstructed meibum had been melted and was able to be squeezed through the opening of the MG ducts. This implied that the MG obstruction was relieved by melting the stagnated lipid of MGs, which subsequently flowed through the ducts and passed out their openings. Consequently, LLTs should be increased as per a report[26] that showed a significant correlation between EMGs and LLTs. Although the present study found that the LipiFlow® treatment resulted in a greater number of EMGs than the warm compresses at each follow-up, those greater

TABLE 3. Comparison of lipid layer thicknesses (LLTs) for both groups and between baseline and at each follow-up for each group.

	LLT scores (mean ± SD)		
	Warm compresses	**LipiFlow®**	**P-value[a]**
Baseline			
Follow-up time	74.9 ± 18.8	70.3 ± 19.9	0.368
1 day	65.4 ± 19.6	65.5 ± 19.0	0.984
Δ mean (95%CI)	-9.4 (-15.6, -3.2)	-6.4 (-13.1, 0.3)	
p-value[b]	0.004	0.062	
1 week	69.0 ± 18.8	65.5 ± 15.9	0.491
Δ mean (95%CI)	-8.5 (-16.1, -0.9)	-5.5 (-15.0, 3.9)	
p-value[b]	0.031	0.238	
1 month	65.0 ± 18.4	69.7 ± 19.9	0.520
Δ mean (95%CI)	-7.6 (-15.7, 0.4)	-2.4 (-12.7, 8.0)	
p-value[b]	0.062	0.630	
6 weeks	73.8 ± 18.0	75.7 ± 16.7	0.798
Δ mean (95%CI)	-1.3 (-15.0, 12.3)	-1.4 (-7.4, 4.6)	
p-value[b]	0.834	0.613	
3 months	80.6 ± 17.8	76.4 ± 13.3	0.491
Δ mean (95%CI)	1.9 (-6.8, 10.7)	5.6 (-5.3, 16.4)	
p-value[b]	0.642	0.286	
6 months	67.1 ± 23.0	66.9 ± 21.2	0.979
Δ mean (95%CI)	-8.0 (-16.9, 0.8)	-2.2 (-12.3, 8.0)	
p-value[b]	0.073	0.662	

[a]comparison of LLT scores for both groups, [b]comparison of LLT scores between baseline and at each follow-up for each group, Δ mean (95%CI) = mean change in LLT scores from baseline to each follow-up for each group (95% confidence interval)

numbers were only statistically significant at the 1-day and 3-month follow-ups. In other words, our study demonstrated that the automated LipiFlow® began to be effective at an earlier time than the warm compresses. As the result of releasing the MG obstruction, LLTs should be evaluated. The current study did not show a statistically significant difference in the LLTs of both groups at baseline and at each follow-up, which is different from the findings of previous studies.[16,27] Although the LLT scores post-LipiFlow® treatment increased insignificantly from baseline, the LLT scores for the warm compress group surprisingly decreased significantly at the 1-day and 1-week follow-ups. This may be due to the small sample size, difficulties in controlling the temperature of the warm compresses, or the enrollment of only patients with a moderate MGD. With that MGD severity, the obstructed meibum needs a higher temperature than the heat provided in a recent program of LipiFlow® and the warm compresses in order to achieve the melting point of the obstructed meibum for severely-affected patients, as reported by Bron et al.[6] and Finis et al.[16] Moreover, the application of the warm compresses needs a great deal of attention to the procedures described in previous studies[3,4] to achieve constant and sufficient heat, and the warm compresses hardly provide a high enough degree of heat to melt the obstructed meibum in patients with moderate to severe MGD. This may explain the surprising result of the significant decrease

in the LLT scores at the 1-day and 1-week follow-ups for the warm compress group. In addition to inadequate temperatures, the formulation of the lipid or meibum in cases of moderate MGD is not normal lipid.[6] Thus, it cannot be easily expressed through the MG duct to its opening to increase the LLT. Even though the results of our study could not show that the effectiveness of the single LipiFlow® treatment was significantly superior to that of the warm compresses, the dry eye symptoms and the number of EMGs of the patients with moderate MGD tended to improve better when they were treated with the LipiFlow® system. The advantages of a single, 12-minute, automated thermodynamic LipiFlow® treatment are that it is less painful than manually expressing the MGs, less time-consuming than the warm compresses, and convenient due to the absence of any self-administered treatment, Moreover, a single treatment has been reported to have a prolonged effect by easing MGD for at least the following 6 months and for up to 3 years.[16-19,28] Nevertheless, the LipiFlow® treatment has several disadvantages: its high cost; the LipiFlow® devices' use of too large an eye cup and lid warmer parts for Asian eyes; and its potentially lower effectiveness for moderate and severe degrees of MGD or MG atrophy, as reported by earlier studies.[16,25,29]

The limitations of this study were its small sample size; a high female to male ratio; the enrollment of only patients with a moderate MGD; no assessment of the tear break-up time; no ocular surface staining; no Schirmer test and an incapacity to monitor the temperature of the hot water and the warm compress procedures performed by the patients at home. There were also disadvantages in having the study eye and the contralateral control eye in the same patient, such as the possibility of an inter-eye interaction and an inability to mask the patients to the specific treatment given to each eye. This may have had some impact on the subjective results, such as the SPEED scores. Since the patients with a moderate severity of MGD had obvious symptoms of dryness, a long follow-up duration of 6 months without any tear supplements might have caused corneal complications. However, the application of the artificial tear eye drops every two hours by the patients in both groups could have improved some of the symptoms of dry eyes, resulting in better SPEED scores being reported by both groups.

On the other hand, the advantages of the present study were that it was a prospective, observer-masked, randomized, controlled clinical trial comparing both treatments in the same patient, which enabled control of the internal factors of both trial groups and provided a long follow-up time of 6 months.

CONCLUSION

The single LipiFlow® treatment and the twice-daily warm compresses relieved the dry eye symptoms of the patients with moderate MGD compared with their baseline symptoms, despite there being no statistical differences in the dry eye symptoms, the number of EMGs, or the LLTs of both treatments.

Further studies should be conducted with a larger sample size and investigated by classifying the patients as having mild, moderate and severe degrees of MGD. In the future, the LipiFlow® system should develop a new program for the treatment of moderate and severe degrees of MGD by slightly increasing the heat or increasing the duration of the treatment or its repetition during a specific time period. Moreover, the eye cup and lid warmer parts of the LipiFlow® system should be available in an optional, smaller size for Asian eyes in order to apply an adequate amount of heat and effectively massage the eyelids.

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