A CLINICAL COMPARISON OF FOUR WARM COMPRESS DEVICES

A thesis presented to the graduate faculty of New England College of Optometry in partial fulfillment of the requirements for the degree of Master of Science

Graham R. Stetson

April 2019

© Graham R. Stetson
All rights reserved.

The author hereby grants New England College of Optometry permission to reproduce and to distribute publicly paper and electronic copies of the thesis document in whole or in part

A CLINICAL COMPARISON OF FOUR WARM COMPRESS DEVICES

Graham R. Stetson

This manuscript has been read and accepted by the Thesis Committee in satisfaction of the thesis requirement for the degree of Master of Science

Date	Amy Nau, OD, FAAO Graduate Faculty Advisor
	Andrew McLeod, OD, FAAO Thesis Committee Member
	Viridiana Kocaba, MD, PhD Thesis Committee Member
	Steven Koevary, PhD Thesis Committee Member
Date	Jane Gwiazda, PhD Director of Graduate Studies

New England College of Optometry

A CLINICAL COMPARISON OF FOUR WARM COMPRESS DEVICES

Graham R. Stetson

New England College of Optometry, 2019

Abstract

Purpose: To evaluate four commercial warm compress devices in their ability to raise inner eyelid surface temperatures (our primary measure of efficacy) to assess post-treatment change in lipid layer thickness as a non-temperature correlate to device efficacy, and to examine how each of these four devices impact corneal topography.

Methods: Subjects (n=9) had each of the four warm compresses applied according to manufacturer recommendations in the following order: Bruder Moist Heat Eye Compress, Thea Belphasteam, MiBo ThermoFlo, TearScience LipiFlow. Measurements of upper and lower, inner and outer eyelid surface temperature, lipid layer thickness, and corneal topography data were obtained both pre- and post-treatment.

Results: LipiFlow increased inner lower eyelid temperature significantly more than the other three devices, and increased inner upper eyelid temperature more on average, though not significantly so, than the other devices as well. Lipid layer thickness was increased most by the Bruder mask and Blephasteam and least by the ThermoFlo. Lipid layer thickness did not correlate with inner eyelid temperature change when measured immediately post-treatment. No significant corneal topography changes occurred with any device.

Conclusion: LipiFlow was the most efficacious device and ThermoFlo was the least efficacious device by the primary efficacy measure. There are still several unknowns in warm compress therapy and treatment of meibomian gland dysfunction.

Table of Contents

INTRODUCTION 6
SUBJECTS 10
MATERIALS AND METHODS 11
Measurement Devices 11
Warm Compresses 11
Statistical Analysis 12
Study Procedures 13
RESULTS 15
Eyelid Temperatures 15
Lipid Layer Thickness 16
Corneal Topography 17
Age Effects 18
DISCUSSION 18
Eyelid Temperatures 18
Lipid Layer Thickness 21
Corneal Topography 24
Age Effects 25
CONCLUSION 25
REFERENCES 38

List of Figures and Tables

Figure 1	The Warm Compresses	27
Table 1	Pre-Treatment Eyelid Temperatures	28
Table 2	Post-Treatment Eyelid Temperatures	29
Table 3	Eyelid Temperature Differences	30
Table 4	Post-Hoc Analysis of Significant Post-Treatment Eyelid Temperatures	31
Table 5	Post-Hoc Analysis of Significant Eyelid Temperature Differences	32
Table 6	Lipid Layer Thicknesses	33
Table 7	Pre-Treatment Corneal Topography Parameters	34
Table 8	Post-Treatment Corneal Topography Parameters	35
Table 9	Differences in Corneal Topography Parameters	36
Table 10	Pre-Treatment Regression by Age	37
Table 11	Post-Treatment Regression by Age	37
Table 12	Pre- and Post-Treatment Differences Regression by Age	37

INTRODUCTION

Dry eye disease (DED) is a condition that presents symptomatically in up to 52.4% of patients while clinical signs of DED are evident in up to 85.6% (Stapleton et al., 2017). These percentages are highest in Southeast Asia, North America, and Western Europe (Stapleton et al., 2017). DED is multifactorial in nature and is characterized by loss of tear film homeostasis (Craig et al., 2017). Meibomian gland dysfunction (MGD), a condition in which meibomian gland secretions are abnormally constituted or are produced in abnormal quantities (Ezuddin, Alawa, & Galor, 2015), is considered to be a leading cause of DED (Nelson et al., 2017). Through the action of a complete blink, the meibomian glands secrete an elaborate array of lipids onto the ocular surface – including wax esters, cholesterol esters, triacylglycerides, and constituents of 14 other lipid classes (Butovich, 2017) – and combined with the mucin and aqueous layers, make up the tear film that serves to nourish, lubricate, protect, and moisturize the surface of the eye (Willcox et al., 2017). When there is an insufficient quantity of meibomian lipids on the ocular surface, as is the case in MGD and most instances of evaporative type DED (Bron et al., 2017), the tear film can become unstable (Willcox et al., 2017). This tear film instability leads to excessive evaporation of the aqueous portion of the tears, increasing tear osmolarity, and culminating in ocular surface inflammation (Bron et al., 2017). This desiccation additionally leads to an irregular primary refracting surface and transitory blurry vision in between blinks (Willcox et al., 2017).

Warm compresses are commonly prescribed as a treatment for the signs and symptoms of MGD (Jones et al., 2017) but compliance among patients is typically short lived. There are an increasing number of commercial devices available that are intended to serve as

surrogates to warm compress therapy (Bitton, Lacroix, & Léger, 2016; Finis et al., 2014; Ishida et al., 2008; Kenrick & Alloo, 2017; Murakami, Blackie, & Korb, 2015; Wang, Gokul, & Craig, 2015). The goal of warm compress treatment is to raise the temperature of the meibomian gland secretions above their melting point (Geerling et al., 2011; Olson, Korb, & Greiner, 2003), thereby increasing liquefaction and improving delivery to and spreading across the ocular surface. The melting temperature of meibum has been shown to be significantly higher in patients with MGD (Borchman et al., 2011; Bron & Tiffany, 2004-a; Geerling et al., 2011; Ong & Larke, 1990). There have been several reported ranges for the melting point of human meibum (from 19.5 to 45°C) (Bron et al., 2004), while other studies have shown there to be a 3.3°C difference in the phase transition of meibum between normals and those with MGD (Borchman et al., 2011). This same study also demonstrated a significantly higher lipid order (stiffness) in the meibum of those with MGD at 33.4°C (Borchman et al., 2011), a temperature between that of the eyelids (~36°C (Blackie et al., 2008)) and the surface of the cornea (~32°C (Morgan, Tullo, & Efron, 1995)). This increased stiffness compounds the effects of increased phase transition temperature in MGD because the increased number of -*trans* configurations along the lipid chains leads to tighter packing and stronger Van der Waal's binding forces, decreasing lipid layer elasticity and rendering the lipids that do reach the tear film less able to spread effectively over the ocular surface (Borchman et al., 2011).

Due to the location of the meibomian glands in the posterior aspect of the eyelid and, in the case of the upper meibomian glands behind the dense collagenous tarsal plate, it can be challenging to apply sufficient external heat to penetrate to the meibomian glands while

preventing thermal injury at the outer eyelid surface (Blackie et al., 2008). This challenge is exacerbated by the fact that heat applied at the outer eyelid surface will also diffuse through the surrounding tissue thereby causing the underlying vasculature to dilate and wick heat away from the area to which it is applied (Despa et al., 2005). Also of concern in warm compress therapy is the desire not to apply excessive heat to the cornea, which lies in apposition to the posterior eyelid surface and has been shown to become increasingly deformable above temperatures of 40°C, though corneal and visual changes have been shown to resolve almost completely 15 minutes after removal of the heat source and have not been examined long-term (McMonnies, Korb, & Blackie, 2012; Solomon et al., 2007).

The purpose of this study was to expand on a previously published report (Kenrick & Alloo, 2017) of these four commercially available warm compress products – two intended for home use and two in-office devices – by observing their effect on inner and outer eyelid temperature and tear lipid layer thickness (LLT). The previous study was a single subject case report in which each of the four devices in this study was utilized in the same order employed here. Only the average of upper and lower inner eyelid temperatures and subjective symptomatology based on a standardized questionnaire were reported. This study expands the number of subjects to better generalize our results. Additional measures were also examined i.e., LLT, outer eyelid temperatures, and corneal topography. Subjective measures of symptomatology were eliminated in this study because of the disconnect between symptomatology and clinical signs (Stapleton et al., 2017), and because this study focuses on the ability of warm compresses to elevate inner eyelid temperature and increase

LLT in individuals independent of their DED status, not improve symptoms or clinical signs of DED or MGD *per se*.

Each of the devices employs methods that attempt to achieve the goal of elevating the temperature of the meibomian glands in different ways. Our hypothesis is that devices applying heat to the outer surface of the eyelids (Bruder mask, ThermoFlo, and Blephasteam, though Blephasteam does not utilize direct contact between heating element and outer eyelid) would be less able to affect inner eyelid temperatures than the device that applies heat directly to the inner eyelids (LipiFlow) (Kenrick & Alloo, 2017). We also hypothesized that LLT changes would correlate with inner eyelid temperature and temperature increase due to the increased liquefaction of meibum at higher temperatures. Changes to corneal topography caused by the warm compress devices were also examined in light of visual degradation and corneal deformation from a combination of heat and pressure applied to the outer eyelids as reported in previous research (Blackie, McMonnies, & Korb, 2013; Lam & Lam, 2007; McMonnies et al., 2012; Solomon et al., 2007). The clinical significance of this research is to enable clinicians to make more informed recommendations regarding warm compress therapeutic intervention for MGD. As temperature is shown to make meibum less viscous and more able to flow, inner eyelid temperature was our primary efficacy measure. Correlation between LLT and inner eyelid temperature and temperature increase was also assessed to evaluate post-therapy LLT change as a possible non-temperature marker of efficacy.

SUBJECTS

This was a prospective, interventional, single site, unmasked pilot study consisting of four study visits. A total of nine healthy subjects without known eye disease (all nine were female, ranging from 28 to 73 years of age, average of 41.4 years, standard deviation 14.7 years) were recruited from a private optometric practice in Massachusetts. Seven of the subjects were of Caucasian ethnicity, one was Asian, and one was of Latin American ethnicity. Two of the subjects were disposable soft contact lens wearers, though they did not wear contact lenses for at least 30 minutes prior to all study visits.

The protocol for this study was approved by New England College of Optometry's Institutional Review Board. Informed consent was obtained prior to initiation of any study procedures.

Inclusion criteria included the following: 18 years of age or older, willing and able to discontinue contact lens use for 30 minutes prior to the study visit, ability to understand instructions and willing and able to attend all study visits, willing and able to discontinue ophthalmic drops or ointments 24 hours prior to the study visit.

Exclusion criteria included the following: Any ocular or systemic medical condition that precluded safe administration of study procedures or would affect the results of the study, ocular or intraocular surgery causing scaring or deformity of the ocular surface, serious ocular trauma in either eye within six months of the study visits, punctal occlusion of any type, current ocular infection or allergic process, use of systemic medication that could contribute to dry eye unless on a stable dosing regimen for 30 days prior to each study visit,

participation in an investigational drug or device study within 30 days of entering the study, use of oil-based cosmetics around the eye, and swimming in a chlorinated pool 12 hours prior to study visits.

MATERIALS AND METHODS

Measurement Devices

Inner and outer eyelid surface temperatures were measured using an Innoo Tech Digital Infrared Thermometer (Innoo Tech, Ningbo, CH), tear film LLT was measured using the LipiView system (TearScience, Morrisville, NC, USA), and corneal topography was assessed using the Keratron Scout (Optikon, Rome, IT).

Warm Compresses

Two warm compresses intended for at-home use were evaluated in this study. The Bruder Moist Heat Eye Compress (Bruder Healthcare, Alpharetta, GA, USA) is a microwavable cloth mask that contains "MediBeads" which absorb ambient moisture between uses and produce a moist heat upon heating ("BRUDER Moist Heat Eye Compress – Bruder Healthcare," n.d.-a; "BRUDER Moist Heat Eye Compress – Bruder Healthcare," n.d.-b; "Moist Heat Therapy Solutions for Dry Eye — Bruder Healthcare Company," n.d.). After microwaving the Bruder device, the compartments containing the "MediBeads" are placed on the closed eyes and the mask is held in place with a hook-and-loop strap. For this study the mask was used without its optional Bruder Hygenic Eyelid Sheets. The Blephasteam (Thea Pharmecuticals, Newcastle under Lyme, UK) is a goggle that is heated electronically. Once preheated, two absorbent fiber rings are moistened with sterile saline and one is inserted into

each half of the goggle ("Blephasteam - Thea Pharmaceuticals," n.d.). The goggle is then placed on the eyes very much like swimming goggles enclosing the eye and eyelids in a hot moist environment.

This study also evaluated two warm compress/meibomian gland expression devices that are intended for in-office use under the supervision of an eyecare professional. The MiBo ThermoFlo (MiBo Medical Group, Plano, TX, USA) features an electronically heated handheld stylus with differently shaped interchangeable metal applicators ("Mibo Medical Group," n.d.). An ultrasound gel is applied to the outer eyelids and the applicator is held against the eyelids and manipulated in a massaging manner throughout the ten-minute treatment session. The LipiFlow (Johnson & Johnson Tear Science, Morrisville, NC, USA) utilizes disposable "activators" that are attached to an electronic base unit. The "activators" consist of a plastic "Cornea Shield" that vaults and insulates the cornea, a heating element on the outer surface of the "Cornea Shield" that is in direct contact with the inner eyelid surface, and two pneumatic bladders that apply pulsed force to the outer eyelid intended to massage heated secretions from the meibomian glands ("LipiFlow Thermal Pulsation System | TearScience," n.d.). See Figure 1 for photographs of each device.

Statistical Analysis

Analysis was conducted using SPSS Statistics 25 (IBM, Armonk, NY, USA). ANOVA models were used to compare measurements across the different treatment modalities and in between subjects. Presence of significant differences between treatments was identified by a test statistic of $p<0.05$ in test of between-subject and between-treatment effects. For

significant between-treatment effects, once identified, Tukey's LSD post-hoc comparisons were utilized to identify the pair or pairs of treatments that differed significantly. For this post-hoc analysis a test statistic of $p<0.05$ was used to determine pairs of observations that were significantly different as well. Best fit regression analysis and ANOVA were used to examine the effect age had on eyelid temperatures and lipid layer thickness. Linear, inverse, and logarithmic regression models were fit to the data and the model with the largest (absolute value) adjusted R squared was chosen to analyze for significance.

Study Procedures

Each of the nine subjects underwent treatment by each of the warm compress devices, one per study session, in the same order, with each study session being no fewer than 12 hours apart (average 31.4 days, standard deviation 37.5 days, minimum 22 hours, maximum 124 days). The first study session utilized the Bruder mask, the second examined the Blephasteam, for the third session the MiBo ThermoFlo was tested, and the LipiFlow was the device examined for the final study session. The LipiFlow was last in order of devices used because previous studies have shown effects of a LipiFlow treatment up to 3 months later (Finis et al., 2014; Zhao et al., 2016). Due to the binocular construction of the Bruder mask and Blephasteam, both eyes received treatment although measurements were only taken for the right eye of each subject. When the ThermoFlo and LipiFlow were being examined only the right eye received treatment.

In each study session, baseline best-corrected visual acuity (BCVA) and anterior segment slit lamp findings were gathered. Corneal topography and LLT pre-treatment measurements

were then determined by equipment in an ancillary testing area of the clinic. The subject was then moved to the treatment room where pre-treatment outer upper eyelid temperature (OULT), outer lower eyelid temperature (OLLT), inner lower eyelid temperature (ILLT), and inner upper eyelid temperature (IULT) measurements were established. Eyelid surface temperatures were all measured by the same investigator and the measurement device was held approximately 1cm away from the eyelid surface being measured in accordance with methodology of previously published protocols (Murakami et al., 2015).

After pre-treatment temperature measurements, the warm compress devices were applied to the subject's right eye, for the ThermoFlo and LipiFlow, or to both eyes, for the Bruder mask and the Blephasteam. For each device, the instructions supplied by the manufacturer were followed. The Bruder mask was microwaved for 20 seconds in an 1100W microwave and was placed on the subject for 10 minutes. The ThermoFlo was similarly applied for the default 10 minutes. The settings for the LipiFlow were likewise not changed from their default settings, and the Blephasteam has settings which cannot be altered.

After the appropriate time period for each device's therapy had ended, the device was removed from the subject, the upper eyelid was everted immediately and its temperature measured. The inner lower eyelid temperature was measured next, followed by the outer lower eyelid temperature and outer upper eyelid temperature. This order was followed because our primary efficacy measure is inner eyelid temperatures and this method allows for the measurement of those temperatures after less time has elapsed from the removal of the warm compress, thereby yielding the most accurate inner eyelid surface temperatures. Total time needed to measure eyelid surface temperatures was less than 30 seconds for all subjects

and devices. Following the acquisition of temperature measurements, the LLT was measured, corneal topography obtained, an anterior segment slit lamp examination was conducted, and BCVA was assessed. Total time for post-treatment evaluation, from the conclusion of warm compress application through final BCVA assessment was less than 10 minutes for all subjects and devices.

RESULTS

Eyelid Temperatures

Pre-treatment eyelid surface temperatures are reported in Table 1. These baseline temperatures were not significantly different before the application of the different warm compresses, with p values ranging from 0.340 to 0.873. There were significant differences in all pre-treatment eyelid temperatures, except IULT, when compared across subjects. This shows that each individual has their own unique eyelid temperatures, except IULT ($p=0.115$), and that these baseline temperatures are consistent for each individual through the four study sessions.

Table 2 displays the post-treatment eyelid temperatures, and Table 3 shows temperature change relative to pre-treatment for each of the treatment types and subjects, respectively. ANOVA analysis shows that post-treatment and differences in OULT, OLLT, and ILLT were significantly different between the four devices, while post-treatment and differences in IULT approached, but did not achieve, statistical significance ($p=0.090$ and $p= 0.068$, respectively). Analysis also indicates that, while each subject had their own unique baseline

eyelid temperatures (except IULT), there was no significant differences between any of the post-treatment eyelid temperatures or difference in eyelid temperatures.

The Tukey's LSD post-hoc analysis for the three significant post-treatment eyelid temperatures (OULT, OLLT, ILLT) is shown in Table 4, and the post-hoc analysis for the three significant temperature differences (OULT, OLLT, ILLT) is shown in Table 5. This analysis shows that the Bruder mask was able to achieve higher OULT than the Blephasteam and ThermoFlo, and higher OLLT that all three other devices. The Bruder was similarly able to increase OULT more than the Blephasteam and ThermoFlo and OLLT more than all three other devices. The LipiFlow was able to generate higher ILLT and increase ILLT more than any of the other three devices in addition to increasing OULT more than the Blephasteam and ThermoFlo.

Lipid Layer Thickness

Pre-treatment, post-treatment, and differences in LLT analyzed by device and by subject are presented in Table 6. The pre-treatment LLT statistics are very similar to pre-treatment eyelid temperatures insofar as there was no difference between pre-treatment LLT when analyzed by device ($p=0.846$) but each individual subject's pre-treatment LLT was unique and relatively consistent at each study session ($p=<0.001$). The post-treatment LLTs differed by more, though not significantly so, between devices ($p=0.364$), but the individual differences remained ($p=0.001$). The inter-device differences were more varied than the inter-subject differences when change in LLT was considered ($p=0.162$ v. $p=0.205$), eliminating the significant inter-subject differences found in pre- and post-treatment LLT.

Corneal Topography

Pre-treatment corneal topography data are displayed in Table 7, post-treatment data in Table 8, and differences between pre- and post-treatment are shown in Table 9. As in pre-treatment eyelid temperatures and LLTs, there were no differences by device for any parameter, while all parameters except cylinder axis were different between subjects. There were still no differences in post-treatment corneal topography parameters or changes to those parameters between device while all parameters were different between subjects post-treatment. Changes to cylinder axis, steep K, and flat eccentricity were significantly different between subjects and steep eccentricity change was close to achieving significance ($p=0.086$).

Each of the subject's BCVAs was 20/20 or better upon entrance to each of the study sessions. Exit BCVAs were the same as entrance BCVAs in all study sessions for all subjects utilizing the same optical correction to achieve entering BCVA. In spite of the different ways in which these devices interface with the cornea and ocular surface, none of these four devices significantly altered any of the topography parameters except the primary astigmatism axis. The direction in which the axes of astigmatism shifted did vary based on whether the device applied pressure directly to the eyelid and indirectly to the cornea. The Bruder mask shifted axis seven times counter-clockwise and once clockwise (when looking at the subject) and the ThermoFlo rotated the astigmatism counter-clockwise six times and clockwise twice. These devices are both intended to apply some pressure to the closed eyelid. The Blephasteam created a shift in axis five times to the counter-clockwise direction and three times counter-clockwise while the LipiFlow created an even split with cylinder axis changing four times in each direction. Each device had one instance in which no change to cylinder axis occurred

and the two devices with roughly equal clockwise and counter-clockwise cylinder rotations had the lowest average cylinder axis change; cylinder axis change is an absolute value in this calculation so clockwise and counter-clockwise rotation do not cancel out.

Age Effects

The effect of age on pre-treatment temperatures and LLT are shown in Table 10, post-treatment data are displayed in Table 11, and analysis of the difference between pre- and post-treatment temperature and LLT are shown in Table 12.

Analysis indicates that eyelid temperatures and LLT increase significantly, though by a small amount, with age (adjusted R squared ranging from 0.174 with IULT to 0.418 with OLLT). Only ILLT was significantly correlated with age post-treatment and its adjusted R squared was 0.091. Eyelid temperature differences were not correlated with age and LLT differences, though not significantly so, were somewhat affected by age ($p=0.056$, adjusted R squared 0.077).

DISCUSSION

Eyelid Temperatures

Each of our subjects had pre-treatment eyelid temperatures, aside from IULT, that differed significantly from each other. Following warm compress application, neither the post-treatment temperatures or change between pre- and post-treatment temperatures differed significantly between subjects. This indicates that the effect on eyelid temperature can be attributed to the individual warm compress devices rather than to differences between the subjects.

Our data show that each of these devices increases inner eyelid temperatures. Our post-hoc analysis shows that the LipiFlow achieved significantly higher ILLT and a greater increase in ILLT than all the other devices. The LipiFlow also demonstrated the highest average IULT (38.4°C) 0.3°C above the next highest average (Blephasteam, 38.1°C). The LipiFlow also increased IULT the most (2.1°C), again by a margin of 0.3°C more than the next greatest increase (Blephasteam, 1.8°C). However, there was no statistical significance in post-treatment IULT and change in IULT between devices ($p=0.090$ and $p=0.068$, respectively). That the LipiFlow resulted in the highest average inner eyelid temperatures and temperature increases makes sense as this device has its heating elements in contact with the inner eyelid surfaces and is programmed to apply a constant 42.5°C throughout the treatment session. The ThermoFlo had the lowest average inner eyelid temperatures and temperature increases and, along with the Bruder mask and Blephasteam, was significantly less effective at changing lower inner eyelid temperatures than the LipiFlow.

None of the devices increased inner eyelid temperature to 40°C, a temperature used by previous research as an efficacy benchmark (Kenrick & Alloo, 2017; Murakami et al., 2015). The inner eyelid temperature results of this study are slightly different than the results of the case report that preceded this study that compares the same four devices (Kenrick & Alloo, 2017). This difference can be ascribed, at least in part, to the fact that the aforementioned case report consisted of a single trial of each of the four devices on a single subject. However, we can draw similar conclusions because the devices that increased inner eyelid temperature the most (LipiFlow) and the least (ThermoFlo) were the same in both studies.

The Bruder mask and Blephasteam increased inner eyelid temperatures fairly equally, and between the averages of the ThermoFlo and LipiFlow, in both studies.

This study has several limitations regarding measuring eyelid temperature, similar to limitations of previous published studies that have utilized similar temperature measurement techniques. To measure any eyelid surface temperature, upper or lower, inner or outer, the source of heat has to be removed from the surface of the closed eye thereby interrupting the flow of thermal energy to the tissues of the eyelid. To measure inner eyelid temperatures, a moist mucous membrane is everted and left exposed, even if momentarily, to evaporative and convective cooling while the measurement is being taken. This prevents creation of an accurate picture of eyelid temperature change and target temperature in warm compress therapy. This also presents a problem in study methodology, because devices like the Bruder mask have been shown to maximally heat the eyelids 2-4 minutes after their application (Murakami et al., 2015), not at the conclusion of the standard treatment cycle (the 10-minute mark in the case of the Bruder mask) this study investigated. Additionally, therapy with the Bruder mask cannot be generalized from this study to normal at home use due to the variance in temperature achieved by the mask in microwaves of different wattages and to the varying ranges of microwaving time (15-20 seconds, 20-25 seconds, and 20-30 seconds) recommended by the manufacturing company itself ("BRUDER Moist Heat Eye Compress – Bruder Healthcare," n.d.-b; "BRUDER Moist Heat Eye Compress – Bruder Healthcare," n.d.-a; "Moist Heat Therapy Solutions for Dry Eye — Bruder Healthcare Company," n.d.). Ideally, measurement of eyelid surface temperatures should occur in real-time without interruption of the flow of heat and exposure of the tissue to environmental cooling forces.

Additionally, to obtain a more comprehensive understanding of how heat is transferred through the eyelid, a constant measurable amount of heat should be utilized as the heat source. Until real-time eyelid surface temperatures can be measured, in the setting of constant controlled heat applied to the outer eyelids, our understanding of how effective eyelid warming therapies can be at heating the meibomian gland secretions will necessarily be limited.

Lipid Layer Thickness

When analyzing LLT by subject we found that pre-treatment and post-treatment LLTs were significantly different between individuals, while the change between pre- and post-treatment LLT was not significantly different between individuals. This indicates that LLT changes from warm compress application cannot be ascribed to differences in individuals but to differences in the compresses themselves.

No one device increased LLT significantly more than any of the others, and LLT change results did not mirror the temperature results, with the Bruder mask and Blephasteam increasing LLT by the largest amount on average though they fell in between the LipiFlow and ThermoFlo in temperature change and post-treatment temperatures. However, the ThermoFlo did increase LLT the least and induced the smallest inner eyelid temperature change resulting in the lowest post-treatment inner eyelid temperatures.

There are several factors involving the therapeutic strategies of the ThermoFlo, LipiFlow, and perhaps even the Bruder mask themselves that possibly influenced the observed LLT changes. The ThermoFlo incorporates the use of an ultrasound gel on the outer eyelids.

Upon completion of the session the ultrasound gel was removed from the eyelids using a facial tissue. It is possible that liquified meibum was perturbed by the tissue along with the ultrasound gel, leading to an erroneously low LLT.

The LipiFlow actively massages the eyelids with pneumatic bladders. This is intended to take advantage of the elevated meibomian gland temperature and evacuate abnormal gland and duct contents as the meibum liquifies. This material is then deposited on the surface of the applicator which is disposed of following the treatment. Thus, any meibum liquified during the therapy is not then present on the ocular surface. Measuring LLT within 5 minutes of termination of treatment could then be expected to show little to no increase in LLT.

The Bruder mask uses a cloth-covered bag of "MediBeads" in direct contact with closed eyelids. It is possible that liquefied meibum may be absorbed by the fabric that is in direct contact with the eyelid surface, decreasing the amount of lipid on the ocular surface. Regardless, the Bruder mask – and other similar warm compress devices – are not intended to express the contents of the meibomian glands *per se* but may otherwise do so by their contact and the pressure exerted on the lid margins. The reusable nature of this product and its ability to absorb substances from the eyelids and lid margins also highlights concerns regarding contamination and infection. One study found that 30 seconds in an 800W microwave was able to reduce *Pseudomonas* bacterial contamination (measured in log number of cells/ml as counted by a hemocytometer), but that even 60 seconds in the same microwave was not able to reduce *Staphylococcus aureus* and *Streptococcus pyogenes* contamination effectively in a similar type of warm compress (Bilkhu et al., 2016).

Our choice of LLT measuring device also had shortcomings that affected the results of the study. Limitations of the LipiView impacted the data and statistics behind LLT and LLT change because the thickest LLT that the device would report was 100nm, regardless how high the LLT was above 100nm. In cases where LLT was above 100nm, an accompanying graphic would show the plot of LLT rising above 100nm, but the scale of the graph was not sufficient to enable us to confidently report another number. Additionally, raw data were not available and the algorithm used to generate the final LLT value reported by the LipiFlow was not known. As such, all LLTs above 100nm were treated as exactly 100nm for statistical purposes. This can be forgiven in the intended diagnostic role of this device because, while there is controversy over normal LLT, it is generally accepted that LLT in individuals symptomatic for DED is below about 75nm (Bron et al., 2004; Isreb et al., 2003; Korb et al., 1994). However, this cap on LLT did affect our results as there were two pre-treatment LLTs (Blephasteam: 1, ThermoFlo:1), and twelve post-treatment LLTs (Bruder: 4, Blephasteam: 5, ThermoFlo: 1, LipiFlow: 2) that were above 100nm and thus led to under-reporting of LLT and LLT change in those instances.

The Blephasteam was the only device that did not come in contact with large areas of the eyelid margin or have the potential to remove lipids from the glands or ocular surface either during or after its therapeutic use. Due to the known and unknown effects of the warm compresses used in this study and the limitations of the LLT reporting range of the LipiView, LLT measurement may not be the best way to test for device efficacy especially immediately following warm compress use. In future studies, at least 2.5 hours should be used as a window between warm compress use and LLT measurement as it has been shown previously

that the recovery time for an optimally secreting meibomian gland is just over two hours (Blackie & Korb, 2009). To assess the long-term effect of therapy, windows of days, weeks, or even months post-treatment should be evaluated. Additionally, while eyelid temperature changes are unlikely to be affected by previous treatments, there is a possibility that previous warm compress therapies may influence future LLT changes induced by warm compresses. To eliminate any influence of previous treatments on subsequent treatments, future studies should randomize the order in which treatments are administered.

Corneal Topography

In spite of small changes in the axis of astigmatism that were found following therapy with each of the four devices, none of the subjects had exiting BCVAs worse than they had at the beginning of each of the study sessions. This, along with the lack of significant changes from baseline in any of the other topography parameters seems to indicate that the temperature of the cornea is not elevated enough by any of these devices to become significantly deformable, at least in a single session. This assertion also has some backing in basic research into the biomechanical properties of porcine corneas, which have been long used as analogs of human corneas. This research found that corneal proteins only begin to denature – and biomechanical properties of the cornea begin to change – at temperatures above 54°C, with the most dramatic changes occurring above 60°C (Kampmeier et al., 2000). Those temperatures would surely be impossible to achieve due to the attendant pain that would ensue (Henriques & Moritz, 1947). One caveat to topography measures is that they only assess surface curvature, future studies utilizing full-thickness corneal measurements might yield different results. Regardless, this finding should be reassuring to clinicians

recommending at-home warm compress therapy with microwavable products because they frequently have little accompanying literature and certainly do not have microwave wattage recommendations like many microwavable meals do at this time.

Age Effects

All eyelid surface temperatures as well as LLT correlated significantly with age pre-treatment, though only ILLT correlated significantly with age post-treatment. Regardless of this significant correlation, its adjusted R squared value was very small (0.091). This shows that, like between-subjects differences in LLT and eyelid temperature, age was not a factor that influence eyelid temperature or LLT in this study. This is also born out in the regression by age of the differences between pre- and post-treatment eyelid temperatures and LLT which showed no significant correlation for any of the measures though LLT differences neared significance ($p=0.056$) with a very small adjusted R squared value (0.077).

CONCLUSION

The eyelid warming device that was most effective at raising inner eyelid temperatures, the primary efficacy measure in this study, was the LipiFlow. The difference between LipiFlow and the other three devices was significant in regards to post-treatment ILLT and ILLT difference. Differences in post-treatment IULT and IULT temperature change were not statistically significant between devices. Post-treatment LLT and change in LLT did not correlate with inner eyelid temperature as was hypothesized. This comparative study is among the first to use only quantifiable objective outcome measures, and is the first published research on the MiBo ThermoFlo. It also provides some direct temperature

evidence for clinicians which may assist them when deciding on which therapeutic intervention to recommend to their patients with MGD. The foregoing notwithstanding, this study had several methodological shortcomings that somewhat limits its applicability. Recommended changes in respect to research design were discussed, as well as gaps in knowledge in warm compress therapy, and areas of concern for the clinician recommending at-home warm compress therapy to their patients.



Figure 1. The Warm Compresses, a) Bruder Moist Heat Eye Compress, b) Thea Blephasteam, c) MiBo ThermoFlo, d) Johnson & Johnson TearScience LipiFow

Table 1. Pre-Treatment Eyelid Temperatures

Pre-Treatment Eyelid Temperatures (°C), Presented as Mean (Standard Error)				
	Pre-Treatment			
Device	**Outer Upper Eyelid Temperature**	**Outer Lower Eyelid Temperature**	**Inner Upper Eyelid Temperature**	**Inner Lower Eyelid Temperature**
Bruder	36.5 (0.084)	36.3 (0.082)	36.3 (0.063)	36.6 (0.086)
Blephasteam	36.5 (0.083)	36.4 (0.073)	36.3 (0.072)	36.5 (0.092)
ThermoFlo	36.5 (0.075)	36.2 (0.073)	36.3 (0.061)	36.5 (0.089)
LipiFlow	36.5 (0.111)	36.2 (0.103)	36.3 (0.062)	36.4 (0.14)
ǂp=	0.873	0.340	0.865	0.663
Subject	**Outer Upper Eyelid Temperature**	**Outer Lower Eyelid Temperature**	**Inner Upper Eyelid Temperature**	**Inner Lower Eyelid Temperature**
1	36.4 (0.087)	36 (0.119)	36.2 (0.087)	36.2 (0.166)
2	36.9 (0.048)	36.3 (0.155)	36.4 (0.075)	36.7 (0.155)
3	36.6 (0.065)	36.4 (0.111)	36.5 (0.041)	36.7 (0.129)
4	36.8 (0.025)	36.4 (0.05)	36.4 (0.095)	36.6 (0.103)
5	36.3 (0.063)	36.1 (0.071)	36.3 (0.131)	36.6 (0.144)
6	36.5 (0.071)	36.5 (0.071)	36.4 (0.103)	36.5 (0.108)
7	36.1 (0.048)	36 (0.025)	36.2 (0.103)	36.2 (0.135)
8	36.4 (0.131)	36.4 (0.129)	36.2 (0.065)	36.4 (0.144)
9	36.5 (0.041)	36.4 (0.063)	36.3 (0)	36.8 (0.048)
ǂp=	**<0.001***	**0.003***	0.115	**0.026***

ǂp Values are Statistics in ANOVA Tests for Differences Between Groups

Table 2. Post-Treatment Eyelid Temperatures

Post-Treatment Eyelid Temperatures (°C), Presented as Mean (Standard Error)				
	Post-Treatment			
Device	**Outer Upper Eyelid Temperature**	**Outer Lower Eyelid Temperature**	**Inner Upper Eyelid Temperature**	**Inner Lower Eyelid Temperature**
Bruder	38.4 (0.229)	37.8 (0.197)	37.9 (0.199)	38.2 (0.181)
Blephasteam	37.6 (0.355)	37 (0.202)	38.1 (0.376)	37.9 (0.183)
ThermoFlo	37 (0.101)	36.7 (0.156)	37.4 (0.236)	37.7 (0.173)
LipiFlow	38.2 (0.099)	37.1 (0.123)	38.4 (0.226)	38.8 (0.193)
[↓]p=	**<0.001***	**0.001***	0.090	**0.002***
Subject	**Outer Upper Eyelid Temperature**	**Outer Lower Eyelid Temperature**	**Inner Upper Eyelid Temperature**	**Inner Lower Eyelid Temperature**
1	37.8 (0.342)	37.5 (0.435)	37.3 (0.692)	37.5 (0.259)
2	38.2 (0.43)	37.4 (0.135)	38.3 (0.189)	38.4 (0.144)
3	37.8 (0.435)	37.3 (0.43)	37.7 (0.295)	38.3 (0.552)
4	38.2 (0.558)	37.4 (0.549)	38.2 (0.263)	38.7 (0.248)
5	38.4 (0.602)	37.1 (0.18)	38.2 (0.451)	38.3 (0.274)
6	37.4 (0.275)	36.9 (0.266)	37.9 (0.343)	38 (0.194)
7	37.4 (0.473)	36.6 (0.307)	37.4 (0.607)	37.8 (0.515)
8	37.4 (0.354)	37 (0.222)	38.4 (0.444)	38 (0.272)
9	37.6 (0.281)	37.4 (0.168)	38.5 (0.206)	38.4 (0.087)
[↓]p=	0.545	0.581	0.415	0.255

[↓]p Values are Statistics in ANOVA Tests for Differences Between Groups

Table 3. Eyelid Temperature Differences

Eyelid Temperature Differences (°C), Presented as Mean (Standard Error)				
	Difference			
Device	**Outer Upper Eyelid Temperature**	**Outer Lower Eyelid Temperature**	**Inner Upper Eyelid Temperature**	**Inner Lower Eyelid Temperature**
Bruder	1.9 (0.199)	1.5 (0.202)	1.7 (0.197)	1.6 (0.155)
Blephasteam	1.1 (0.348)	0.6 (0.225)	1.8 (0.321)	1.4 (0.17)
ThermoFlo	0.5 (0.088)	0.6 (0.176)	1.1 (0.221)	1.2 (0.165)
LipiFlow	1.7 (0.144)	0.9 (0.127)	2.1 (0.247)	2.3 (0.227)
ǂ**p=**	**<0.001***	**0.005***	0.068	**0.001***
Subject	**Outer Upper Eyelid Temperature**	**Outer Lower Eyelid Temperature**	**Inner Upper Eyelid Temperature**	**Inner Lower Eyelid Temperature**
1	1.5 (0.425)	1.5 (0.349)	1.2 (0.743)	1.3 (0.392)
2	1.3 (0.421)	1.1 (0.217)	2 (0.119)	1.7 (0.025)
3	1.2 (0.453)	0.9 (0.504)	1.2 (0.307)	1.6 (0.665)
4	1.4 (0.563)	1.1 (0.501)	1.8 (0.216)	2.1 (0.214)
5	2.1 (0.555)	1 (0.118)	1.9 (0.373)	1.8 (0.343)
6	0.9 (0.221)	0.4 (0.256)	1.5 (0.295)	1.5 (0.166)
7	1.2 (0.497)	0.6 (0.32)	1.2 (0.506)	1.6 (0.507)
8	1 (0.338)	0.5 (0.222)	2.2 (0.381)	1.5 (0.371)
9	1.1 (0.259)	1 (0.17)	2.2 (0.206)	1.6 (0.075)
ǂ**p=**	0.695	0.399	0.313	0.916

ǂp Values are Statistics in ANOVA Tests for Differences Between Groups

Table 4. Post-Hoc Analysis of Significant Post-Treatment Eyelid Temperatures

Significant Post-Treatment Temperatures			
Outer Upper Eyelid			
A	B	Mean Difference (A-B)	Sig.
Bruder	Blephasteam	**.8333***	**0.012**
	ThermoFlo	**1.4333***	**<0.001**
	LipiFlow	0.2556	0.423
Blephasteam	Bruder	**-.8333***	**0.012**
	ThermoFlo	0.6000	0.066
	LipiFlow	-0.5778	0.076
ThermoFlo	Bruder	**-1.4333***	**<0.001**
	Blephasteam	-0.6000	0.066
	LipiFlow	**-1.1778***	**0.001**
LipiFlow	Bruder	-0.2556	0.423
	Blephasteam	0.5778	0.076
	ThermoFlo	**1.1778***	**0.001**
Outer Lower Eyelid			
A	B	Mean Difference (A-B)	Sig.
Bruder	Blephasteam	**.8444***	**0.002**
	ThermoFlo	**1.0889***	**<0.001**
	LipiFlow	**.7222***	**0.006**
Blephasteam	Bruder	**-.8444***	**0.002**
	ThermoFlo	0.2444	0.324
	LipiFlow	-0.1222	0.620
ThermoFlo	Bruder	**-1.0889***	**<0.001**
	Blephasteam	-0.2444	0.324
	LipiFlow	-0.3667	0.143
LipiFlow	Bruder	**-.7222***	**0.006**
	Blephasteam	0.1222	0.620
	ThermoFlo	0.3667	0.143
Inner Lower Eyelid			
A	B	Mean Difference (A-B)	Sig.
Bruder	Blephasteam	0.2333	0.373
	ThermoFlo	0.5000	0.062
	LipiFlow	**-.5889***	**0.029**
Blephasteam	Bruder	-0.2333	0.373
	ThermoFlo	0.2667	0.309
	LipiFlow	**-.8222***	**0.003**
ThermoFlo	Bruder	-0.5000	0.062
	Blephasteam	-0.2667	0.309
	LipiFlow	**-1.0889***	**<0.001**
LipiFlow	Bruder	**.5889***	**0.029**
	Blephasteam	**.8222***	**0.003**
	ThermoFlo	**1.0889***	**<0.001**

Table 5. Post-Hoc Analysis of Significant Eyelid Temperature Differences

Significant Eyelid Temperature Differences			
Outer Upper Eyelid			
A	B	Mean Difference (A-B)	Sig.
Bruder	Blephasteam	**.8111***	**0.013**
	ThermoFlo	**1.3556***	**<0.001**
	LipiFlow	0.1667	0.592
Blephasteam	Bruder	**-.8111***	**0.013**
	ThermoFlo	0.5444	0.086
	LipiFlow	**-.6444***	**0.044**
ThermoFlo	Bruder	**-1.3556***	**<0.001**
	Blephasteam	-0.5444	0.086
	LipiFlow	**-1.1889***	**0.001**
LipiFlow	Bruder	-0.1667	0.592
	Blephasteam	**.6444***	**0.044**
	ThermoFlo	**1.1889***	**0.001**
Outer Lower Eyelid			
A	B	Mean Difference (A-B)	Sig.
Bruder	Blephasteam	**.8556***	**0.003**
	ThermoFlo	**.9333***	**0.001**
	LipiFlow	**.5778***	**0.036**
Blephasteam	Bruder	**-.8556***	**0.003**
	ThermoFlo	0.0778	0.770
	LipiFlow	-0.2778	0.300
ThermoFlo	Bruder	**-.9333***	**0.001**
	Blephasteam	-0.0778	0.770
	LipiFlow	-0.3556	0.187
LipiFlow	Bruder	**-.5778***	**0.036**
	Blephasteam	0.2778	0.300
	ThermoFlo	0.3556	0.187
Inner Lower Eyelid			
A	B	Mean Difference (A-B)	Sig.
Bruder	Blephasteam	0.1111	0.668
	ThermoFlo	0.3667	0.162
	LipiFlow	**-.7667***	**0.005**
Blephasteam	Bruder	-0.1111	0.668
	ThermoFlo	0.2556	0.326
	LipiFlow	**-.8778***	**0.002**
ThermoFlo	Bruder	-0.3667	0.162
	Blephasteam	-0.2556	0.326
	LipiFlow	**-1.1333***	**<0.001**
LipiFlow	Bruder	**.7667***	**0.005**
	Blephasteam	**.8778***	**0.002**
	ThermoFlo	**1.1333***	**<0.001**

Table 6. Lipid Layer Thicknesses

Lipid Layer Thicknesses (nm), Presented as Mean (Standard Error)			
Device	**Pre-Treatment**	**Post-Treatment**	**Difference**
Bruder	55.7 (4.1)	76.3 (7.6)	20.7 (7.6)
Blephasteam	62.1 (7.1)	81.1 (7.8)	19 (5.8)
ThermoFlo	62.2 (7.2)	63.1 (7.8)	0.9 (3.2)
LipiFlow	62.4 (6.4)	77.4 (6.8)	15 (8.7)
ǂ**p=**	0.846	0.364	0.162
Subject	**Pre-Treatment**	**Post-Treatment**	**Difference**
1	94 (5)	99.8 (0.3)	5.8 (5.2)
2	46.5 (1)	50.8 (4.4)	4.3 (3.9)
3	48 (2.1)	57 (3.5)	9 (2.3)
4	62.3 (7.5)	85.8 (8.6)	23.5 (15.4)
5	64.3 (5.9)	61.8 (3.5)	-2.5 (7.6)
6	64 (8.8)	93.8 (6.3)	29.8 (12.8)
7	40.5 (3.4)	56.3 (12.2)	15.8 (12.6)
8	71.3 (6.9)	79.3 (10.4)	8 (9.3)
9	54.8 (6.9)	86.3 (13.8)	31.5 (10.5)
ǂ**p=**	**<0.001***	**0.001***	0.205

ǂp Values are Statistics in ANOVA Tests for Differences Between Groups

Table 7. Pre-Treatment Corneal Topography Parameters

Pre-Treatment Corneal Parameters, Presented as Mean (Standard Error)						
	Pre-Treatment					
Device	**Flat K (D)**	**Cylinder Axis**	**Steep K (D)**	**Cylinder Power (D)**	**Flat Eccentricity**	**Steep Eccentricity**
Bruder	43.69 (0.481)	151.78 (13.949)	44.75 (0.346)	1.06 (0.333)	0.4 (0.045)	0.39 (0.04)
Blephasteam	43.64 (0.449)	99 (26.196)	44.64 (0.382)	1 (0.311)	0.42 (0.036)	0.41 (0.041)
ThermoFlo	43.8 (0.492)	112.67 (26.41)	44.86 (0.414)	1.07 (0.333)	0.36 (0.053)	0.29 (0.113)
LipiFlow	43.62 (0.516)	101.56 (25.778)	44.73 (0.384)	1.11 (0.313)	0.38 (0.022)	0.41 (0.046)
[4]**p=**	0.994	0.378	0.982	0.997	0.761	0.513
Subject	**Flat K (D)**	**Cylinder Axis**	**Steep K (D)**	**Cylinder Power (D)**	**Flat Eccentricity**	**Steep Eccentricity**
1	44.26 (0.074)	108 (5.583)	44.43 (0.119)	0.18 (0.052)	0.46 (0.029)	0.38 (0.013)
2	44.49 (0.223)	167.5 (4.907)	45.59 (0.247)	1.1 (0.046)	0.34 (0.037)	0.17 (0.217)
3	46.32 (0.057)	54.75 (39.765)	46.58 (0.093)	0.26 (0.073)	0.39 (0.021)	0.25 (0.056)
4	44.09 (0.104)	135.75 (43.256)	44.91 (0.076)	0.82 (0.049)	0.63 (0.038)	0.36 (0.073)
5	44.44 (0.059)	57.25 (11.176)	44.81 (0.066)	0.37 (0.054)	0.28 (0.056)	0.32 (0.082)
6	42 (0.127)	132.75 (43.929)	44.93 (0.073)	2.94 (0.067)	0.42 (0.023)	0.48 (0.047)
7	43.1 (0.149)	132.25 (43.82)	43.73 (0.069)	0.62 (0.096)	0.3 (0.033)	0.31 (0.03)
8	41.69 (0.14)	167.5 (3.926)	42.57 (0.145)	0.88 (0.053)	0.36 (0.047)	0.48 (0.036)
9	42.81 (0.089)	90.5 (50.814)	45.18 (0.074)	2.37 (0.033)	0.36 (0.026)	0.63 (0.021)
[4]**p=**	**<0.001***	0.177	**<0.001***	**<0.001***	**<0.001***	**0.036***

[4]p Values are Statistics in ANOVA Tests for Differences Between Groups

Table 8. Post-Treatment Corneal Topography Parameters

Post-Treatment Corneal Parameters, Presented as Mean (Standard Error)						
	Post-Treatment					
Device	**Flat K (D)**	**Cylinder Axis**	**Steep K (D)**	**Cylinder Power (D)**	**Flat Eccentricity**	**Steep Eccentricity**
Bruder	43.65 (0.477)	119.56 (23.267)	44.82 (0.349)	1.16 (0.3)	0.37 (0.052)	0.46 (0.042)
Blephasteam	43.7 (0.482)	100.56 (25.208)	44.73 (0.353)	1.02 (0.31)	0.4 (0.041)	0.35 (0.061)
ThermoFlo	43.63 (0.479)	104.78 (27.366)	44.78 (0.344)	1.15 (0.32)	0.37 (0.044)	0.36 (0.069)
LipiFlow	43.62 (0.439)	80.67 (24.435)	44.67 (0.363)	1.04 (0.325)	0.4 (0.041)	0.31 (0.114)
ǂ**p=**	0.999	0.748	0.991	0.985	0.942	0.599
Subject	**Flat K (D)**	**Cylinder Axis**	**Steep K (D)**	**Cylinder Power (D)**	**Flat Eccentricity**	**Steep Eccentricity**
1	44.3 (0.078)	119.25 (11.485)	44.7 (0.175)	0.4 (0.125)	0.38 (0.024)	0.49 (0.037)
2	44.19 (0.235)	120.25 (39.976)	45.18 (0.191)	1 (0.126)	0.36 (0.023)	0.37 (0.088)
3	46.26 (0.162)	98.75 (44.455)	46.6 (0.064)	0.34 (0.125)	0.33 (0.035)	0.07 (0.097)
4	44.18 (0.109)	4.25 (1.181)	45.13 (0.117)	0.95 (0.163)	0.64 (0.023)	0.51 (0.055)
5	44.24 (0.111)	76.5 (1.5)	44.63 (0.053)	0.39 (0.12)	0.42 (0.017)	0.39 (0.035)
6	41.92 (0.125)	176.25 (1.436)	44.75 (0.117)	2.84 (0.056)	0.46 (0.012)	0.45 (0.018)
7	43.29 (0.108)	49.5 (34.241)	43.87 (0.095)	0.58 (0.09)	0.25 (0.062)	0.04 (0.16)
8	41.86 (0.082)	131.25 (43.425)	42.77 (0.104)	0.91 (0.07)	0.28 (0.067)	0.45 (0.041)
9	42.67 (0.079)	136.5 (43.5)	45.13 (0.039)	2.46 (0.074)	0.35 (0.04)	0.59 (0.024)
ǂ**p=**	**<0.001***	**0.023***	**<0.001***	**<0.001***	**<0.001***	**<0.001***

ǂp Values are Statistics in ANOVA Tests for Differences Between Groups

Table 9. Differences in Corneal Topography Parameters

Corneal Parameter Differences, Presented as Mean (Standard Error)						
	Difference					
Device	**Flat K (D)**	**Cylinder Axis**	**Steep K (D)**	**Cylinder Power (D)**	**Flat Eccentricity**	**Steep Eccentricity**
Bruder	-0.03 (0.06)	13.78 (4.443)	0.07 (0.109)	0.1 (0.077)	-0.03 (0.035)	0.07 (0.029)
Blephasteam	0.07 (0.077)	11.78 (2.808)	0.09 (0.101)	0.02 (0.069)	-0.02 (0.03)	-0.07 (0.038)
ThermoFlo	-0.16 (0.086)	14.11 (6.095)	-0.08 (0.113)	0.08 (0.09)	0.01 (0.045)	0.08 (0.097)
LipiFlow	0 (0.153)	8.67 (2.489)	-0.06 (0.09)	-0.06 (0.104)	0.02 (0.023)	-0.09 (0.116)
ǂ**p=**	0.447	0.788	0.577	0.545	0.665	0.304
Subject	**Flat K (D)**	**Cylinder Axis**	**Steep K (D)**	**Cylinder Power (D)**	**Flat Eccentricity**	**Steep Eccentricity**
1	0.04 (0.104)	28.25 (6.7)	0.27 (0.18)	0.23 (0.1)	-0.08 (0.05)	0.11 (0.035)
2	-0.3 (0.143)	12.25 (3.544)	-0.41 (0.116)	-0.11 (0.161)	0.02 (0.021)	0.2 (0.159)
3	-0.06 (0.178)	11.5 (4.873)	0.02 (0.153)	0.08 (0.124)	-0.06 (0.034)	-0.18 (0.149)
4	0.09 (0.147)	4.5 (1.848)	0.22 (0.138)	0.13 (0.132)	0.01 (0.051)	0.15 (0.107)
5	-0.2 (0.125)	19.25 (9.953)	-0.18 (0.107)	0.02 (0.165)	0.14 (0.058)	0.06 (0.085)
6	-0.08 (0.032)	2 (1.683)	-0.18 (0.081)	-0.1 (0.098)	0.04 (0.017)	-0.03 (0.037)
7	0.18 (0.233)	20.75 (2.462)	0.14 (0.115)	-0.04 (0.172)	-0.05 (0.028)	-0.27 (0.172)
8	0.17 (0.078)	8.75 (4.837)	0.2 (0.103)	0.03 (0.108)	-0.08 (0.065)	-0.03 (0.073)
9	-0.14 (0.164)	1.5 (0.645)	-0.05 (0.091)	0.09 (0.1)	-0.01 (0.031)	-0.04 (0.044)
ǂ**p=**	0.270	**0.007***	**0.009***	0.696	**0.027***	0.086

ǂp Values are Statistics in ANOVA Tests for Differences Between Groups

Table 10. Pre-Treatment Regression by Age

Pre-Treatment Regression Analysis by Age					
	Best Fit Model	**R Squared**	**Adjusted R Squared**	**Standard Error of the Estimate**	**ANOVA p=**
OULT	Inverse	0.356	0.337	0.210	***<0.001**
OLLT	Logarithmic	0.435	0.418	0.193	***<0.001**
IULT	Inverse	0.198	0.174	0.170	***0.007**
ILLT	Logarithmic	0.201	0.178	0.278	***0.006**
LLT	Linear	0.262	0.240	16.052	***0.001**

Table 11. Post-Treatment Regression by Age

Post-Treatment Regression Analysis by Age					
	Best Fit Model	**R Squared**	**Adjusted R Squared**	**Standard Error of the Estimate**	**ANOVA p=**
OULT	Inverse	0.004	-0.026	0.861	0.730
OLLT	Linear	0.000	-0.029	0.653	0.956
IULT	Linear	0.052	0.024	0.839	0.182
ILLT	Logarithmic	0.117	0.091	0.633	***0.041**
LLT	Inverse	0.001	-0.028	22.912	0.840

Table 12. Pre- and Post-Treatment Differences Regression by Age

Difference Regression Analysis by Age					
	Best Fit Model	**R Squared**	**Adjusted R Squared**	**Standard Error of the Estimate**	**ANOVA p=**
OULT	Linear	0.064	0.037	0.814	0.135
OLLT	Linear	0.069	0.042	0.637	0.121
IULT	Inverse	0.015	-0.014	0.809	0.474
ILLT	Inverse	0.018	-0.011	0.677	0.434
LLT	Inverse	0.103	0.077	19.826	0.056

REFERENCES

Bilkhu, P., Wolffsohn, J. S., Hilton, A., Matthews, G., Legood, S., & Riley, L. (2016). Microwave decontamination of eyelid warming devices for the treatment of meibomian gland dysfunction. *Contact Lens and Anterior Eye*, *39*(4), 293–297. https://doi.org/10.1016/j.clae.2015.12.001

Bitton, E., Lacroix, Z., & Léger, S. (2016). In-vivo heat retention comparison of eyelid warming masks. *Contact Lens and Anterior Eye*, *39*(4), 311–315. https://doi.org/10.1016/j.clae.2016.04.002

Blackie, C. A., McMonnies, C. W., & Korb, D. R. (2013). Warm compresses and the risks of elevated corneal temperature with massage. *Cornea*, *32*(7), e146-9. https://doi.org/10.1097/ICO.0b013e318292a7b7

Blackie, C. A., Solomon, J. D., Greiner, J. V, Holmes, M., & Korb, D. R. (2008). Inner eyelid surface temperature as a function of warm compress methodology. *Optometry and Vision Science : Official Publication of the American Academy of Optometry*, *85*(8), 675–683. https://doi.org/10.1097/OPX.0b013e318181adef

Blackie, C. a, & Korb, D. R. (2009). Recovery time of an optimally secreting meibomian gland. *Cornea*, *28*(3), 293–297. https://doi.org/10.1097/ICO.0b013e31818913b4

Blephasteam - Thea Pharmaceuticals. (n.d.). Retrieved February 16, 2019, from https://www.thea-pharmaceuticals.co.uk/products/blephasteam

Borchman, D., Foulks, G. N., Yappert, M. C., Bell, J., Wells, E., Neravetla, S., & Greenstone, V. (2011). Human meibum lipid conformation and thermodynamic changes with meibomian-gland dysfunction. *Investigative Ophthalmology and Visual Science*, *52*(6), 3805–3817. https://doi.org/10.1167/iovs.10-6514

Bron, A. J., & Tiffany, J. M. (2004). The contribution of meibomian disease to dry eye. *Ocular Surface*, *2*(2), 149–164. https://doi.org/10.1016/S1542-0124(12)70150-7

Bron, A. J., Tiffany, J. M., Gouveia, S. M., Yokoi, N., & Voon, L. W. (2004). Functional aspects of the tear film lipid layer. *Experimental Eye Research*, *78*(3), 347–360. https://doi.org/10.1016/j.exer.2003.09.019

Bron, Anthony J., de Paiva, C. S., Chauhan, S. K., Bonini, S., Gabison, E. E., Jain, S., … Sullivan, D. A. (2017). TFOS DEWS II pathophysiology report. *Ocular Surface*, *15*(3), 438–510. https://doi.org/10.1016/j.jtos.2017.05.004

BRUDER Moist Heat Eye Compress – Bruder Healthcare. (n.d.-a). Retrieved February 10, 2017, from https://shop.bruder.com/collections/eye-care/products/bruder-moist-heat-eye-compress

BRUDER Moist Heat Eye Compress – Bruder Healthcare. (n.d.-b). Retrieved July 11, 2017, from https://shop.bruder.com/products/bruder-moist-heat-eye-compress

Butovich, I. A. (2017). Meibomian glands, meibum, and meibogenesis. *Experimental Eye Research*, *163*, 2–16. https://doi.org/10.1016/j.exer.2017.06.020

Craig, J. P., Nichols, K. K., Akpek, E. K., Caffery, B., Dua, H. S., Joo, C. K., … Stapleton, F. (2017). TFOS DEWS II Definition and Classification Report. *Ocular Surface*, *15*(3), 276–283. https://doi.org/10.1016/j.jtos.2017.05.008

Despa, F., Orgill, D. P., Neuwalder, J., & Lee, R. C. (2005). The relative thermal stability of tissue macromolecules and cellular structure in burn injury. *Burns*, *31*(5), 568–577. https://doi.org/10.1016/j.burns.2005.01.015

Ezuddin, N. S., Alawa, K. A., & Galor, A. (2015). Therapeutic Strategies to Treat Dry Eye in an Aging Population. *Drugs and Aging*, *32*(7), 505–513. https://doi.org/10.1007/s40266-015-0277-

6

Finis, D., Hayajneh, J., König, C., Borrelli, M., Schrader, S., & Geerling, G. (2014). Evaluation of an automated thermodynamic treatment (Lipiflow®) system for meibomian gland dysfunction: A prospective, randomized, observer-masked trial. *The Ocular Surface*, *12*(2), 146–154. https://doi.org/10.1016/j.jtos.2013.12.001

Geerling, G., Tauber, J., Baudouin, C., Goto, E., Matsumoto, Y., O'Brien, T., … Nichols, K. K. (2011). The International Workshop on Meibomian Gland Dysfunction: Report of the Subcommittee on Management and Treatment of Meibomian Gland Dysfunction. *Investigative Ophthalmology & Visual Science*, *52*(4), 2050. https://doi.org/10.1167/iovs.10-6997g

Henriques, F. C., & Moritz, A. R. (1947). Studies of thermal injury II. the relative importance of time and surface temperature in the causation of cutaneous burns. *American Journal of Pathology*, *23*(5), 695–720.

Ishida, R., Matsumoto, Y., Onguchi, T., Kaido, M., Iwamuro, K., Kobayashi, J., … Tsubota, K. (2008). Tear film with "Orgahexa EyeMasks" in patients with meibomian gland dysfunction. *Optometry and Vision Science*, *85*(8), 684–691. https://doi.org/10.1097/OPX.0b013e318181ae83

Isreb, M., Greiner, J., Korb, D., Glonek, T., Mody, S., Finnemore, V., & Reddy, C. (2003). Correlation of lipid layer thickness measurements with fluorescein tear film break-up time and Schirmer's test. *Eye*, *17*, 79–83. https://doi.org/10.1038/sj.eye.6700224

Jones, L., Downie, L. E., Korb, D., Benitez-del-Castillo, J. M., Dana, R., Deng, S. X., … Craig, J. P. (2017). TFOS DEWS II Management and Therapy Report. *Ocular Surface*, *15*(3), 575–628. https://doi.org/10.1016/j.jtos.2017.05.006

Kampmeier, J., Radt, B., Birngruber, R., & Brinkmann, R. (2000). Thermal and biomechanical parameters of porcine cornea. *Cornea*, *19*(3), 355–363. https://doi.org/10.1097/00003226-200005000-00020

Kenrick, C. J., & Alloo, S. S. (2017). The Limitation of Applying Heat to the External Lid Surface: A Case of Recalcitrant Meibomian Gland Dysfunction. *Case Rep Ophthalmol*, *8*, 7–12. https://doi.org/10.1159/000455087

Korb, D. R., Baron, D. F., Herman, J. P., Finnemore, V. M., Exford, J. M., Hermosa, J. L., … Greiner, J. V. (1994). Tear Film Lipid Layer Thickness as a Function of Blinking. *Cornea*, *13*(4), 354–359.

Lam, A. K. C., & Lam, C. H. (2007). Effect of warm compress therapy from hard-boiled eggs on corneal shape. *Cornea*, *26*(2), 163–167. https://doi.org/10.1097/01.ico.0000248380.86401.4d

LipiFlow Thermal Pulsation System | TearScience. (n.d.). Retrieved February 16, 2019, from https://tearscience.com/lipiflow/

McMonnies, C. W., Korb, D. R., & Blackie, C. A. (2012). The role of heat in rubbing and massage-related corneal deformation. *Contact Lens and Anterior Eye*, *35*(4), 148–154. https://doi.org/10.1016/j.clae.2012.01.001

Mibo Medical Group. (n.d.). Retrieved February 16, 2019, from http://mibomedicalgroup.com/mibothermoflo.html

Moist Heat Therapy Solutions for Dry Eye — Bruder Healthcare Company. (n.d.). Retrieved February 10, 2017, from https://www.bruder.com/eye-care-educational-resources/2016/3/28/moist-heat-therapy-solutions-for-dry-eye

Morgan, P., Tullo, A., & Efron, N. (1995). Infrared thermography of the tear film in dry eye. *Eye*, *9*,

615–618. https://doi.org/10.1038/eye.1995.149

Murakami, D. K., Blackie, C. A., & Korb, D. R. (2015). All Warm Compresses Are Not Equally Efficacious. *Optometry and Vision Science : Official Publication of the American Academy of Optometry*, *92*(9), e327-33. https://doi.org/10.1097/OPX.0000000000000675

Nelson, J. D., Craig, J. P., Akpek, E. K., Azar, D. T., Belmonte, C., Bron, A. J., … Sullivan, D. A. (2017). TFOS DEWS II Introduction. *Ocular Surface*, *15*(3), 269–275. https://doi.org/10.1016/j.jtos.2017.05.005

Olson, M. C., Korb, D. R., & Greiner, J. V. (2003). Increase in tear film lipid layer thickness following treatment with warm compresses in patients with meibomian gland dysfunction. *Eye and Contact Lens*, *29*(2), 96–99. https://doi.org/10.1097/01.ICL.0000060998.20142.8D

Ong, B. L., & Larke, J. R. (1990). Meibomian gland dysfunction: some clinical, biochemical and physical observations. *Ophthalmic & Physiological Optics : The Journal of the British College of Ophthalmic Opticians (Optometrists)*, *10*(2), 144–148. https://doi.org/10.1111/j.1475-1313.1990.tb00968.x

Solomon, J. D., Case, C. L., Greiner, J. V, Blackie, C. A., Herman, J. P., & Korb, D. R. (2007). Warm compress induced visual degradation and Fischer-Schweitzer polygonal reflex. *Optometry and Vision Science*, *84*(7), 580–587. https://doi.org/10.1097/OPX.0b013e3180dc99d5

Stapleton, F., Alves, M., Bunya, V. Y., Jalbert, I., Lekhanont, K., Malet, F., … Jones, L. (2017). TFOS DEWS II Epidemiology Report. *Ocular Surface*, *15*(3), 334–365. https://doi.org/10.1016/j.jtos.2017.05.004

Wang, M. T. M., Gokul, A., & Craig, J. P. (2015). Temperature profiles of patient-applied eyelid warming therapies. *Contact Lens and Anterior Eye*, *38*(6), 430–434.

https://doi.org/10.1016/j.clae.2015.06.002

Willcox, M. D. P., Argüeso, P., Georgiev, G. A., Holopainen, J. M., Laurie, G. W., Millar, T. J., … Jones, L. (2017). TFOS DEWS II Tear Film Report. *Ocular Surface*, *15*(3), 366–403. https://doi.org/10.1016/j.jtos.2017.03.006

Zhao, Y., Veerappan, A., Yeo, S., Rooney, D. M., Acharya, R. U., Tan, J. H., & Tong, L. (2016). Clinical trial of thermal pulsation (LipiFlow) in meibomian gland dysfunction with preteatment meibography. *Eye and Contact Lens, 42*(6), 339–346. https://doi.org/10.1097/ICL.0000000000000228