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Comparison of treatment effect across varying severities of meibomian gland dropout

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ABSTRACT

Purpose: Better understanding of the pathophysiology of meibomian gland dysfunction (MGD) has provided the opportunity to develop treatments which could be tailored for specific presentations of MGD. This study sought to directly compare treatment effectiveness for three current therapies across differing levels of MG dropout.

Methods: Subjects (n = 81), grouped by infrared meibography dropout proportions, into either no (control), mild, or pronounced MG dropout, were randomised to receive treatment with a latent heat device (n = 25), liposomal spray (n = 28), or heated warm compress (n = 28). A battery of tear film measures was performed, pre- and post-application of treatment, and compared by treatment type and MG severity.

Results: Symptoms correlated with MG dropout proportions ($r = 0.618$, $p < 0.001$). Following treatment, non-invasive tear breakup time improved ($p = 0.010$), independent of treatment type ($p = 0.131$). The improvement was significant only in the pronounced MGD group ($+4.32 \pm 1.15s$, $p = 0.008$), however, following treatment, the mild group was no longer distinct from the control group ($p = 0.843$). Lipid layer grade (LLG) also improved following treatment ($p < 0.009$), but again was not specific to treatment type ($p = 0.349$). All three severity groups showed an improvement in LLG, with 49.3% of participants showing an improvement of at least one grade, and none showing decreased LLG.

Conclusions: Increased LLG across all three treatment groups suggests that all methods increase meibum outflow to the tear film, resulting in a thicker lipid layer after treatment. These results suggest that all three treatments are effective in improving tear film quality, independent of MGD severity based either on symptoms or based on gland dropout.

1. Introduction

Meibomian gland dysfunction (MGD) is a leading cause of dry eye, affecting around 33% of people younger than 30 years old, and increasing significantly with age [1]. The early stages of MGD show hyper-keratinisation of the MG duct, and meibum with reduced outflow [2], modified composition [3], and increased melting point. As the disease progresses, meibum outflow further decreases, leading to complete stasis of oils from the gland, and to MG atrophy, observed clinically as loss of the gland (MG dropout). Common treatment paradigms typically focus on either raising the gland temperature or clearing the ducts, to improve meibum outflow, or applying artificial ophthalmic products to supplement the natural tear film [4]. Whether success of these modalities corresponds to different severity stages is not currently known.

Eyelid warming systems, such as latent heat goggles and heated seed

or bead pouches aim to increase MG function by raising the local temperature to help liquefy the meibum [5], facilitate output into the tear film [2], and potentially provide a barrier to evaporation. Goggles create a closed microclimate in the periocular area [6], which is believed to further reduce aqueous evaporation [7]. Liposomal sprays work by migration of phospholipids across the lid margin to combine with natural lipids and increase the lipid layer thickness and stability [8], and have previously been shown to be more effective than hyaluronate eye drops and triglyceride gel at restoring tear film stability [9,10].

This study aimed to compare the effectiveness of a single application of three MGD interventions; latent heat device, warm compresses, and liposomal spray, in sex-matched individuals with differing levels of MG dropout.

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Table 1

Distribution of three MGD severity groups between the three treatment cohorts: latent heat device, liposomal spray, and heated eyebag. The distribution of McMonnies Dry Eye Questionnaire scores was significantly increased with each MGD severity group ($F = 54.27$, $p < 0.001$). Meibomian gland (MG) dropout was also significantly different between each severity group ($F = 279.38$, $p < 0.001$).

MG dropout group	Age (years)	McMonnies Score	MG Dropout (%)	Latent Heat	Liposomal Spray	Heated Eyebag	Total
Control ($\leq 5\%$)	36 \pm 15	6.76 \pm 4.30	3.81 \pm 2.18	6	8	7	21
Mild (5–40%)	42 \pm 16	17.19 \pm 5.43	17.14 \pm 8.33	11	8	8	27
Pronounced ($\geq 40\%$)	55 \pm 16	22.45 \pm 5.98	75.94 \pm 15.05	8	12	13	33
Total	46 \pm 18	16.63 \pm 8.26	36.91 \pm 33.85	25	28	28	81

2. Methods

A total of 81 participants (56% female, age 46 \pm 18 years, range 23–89 years) were enrolled in a prospective, single-visit, randomised cohort study of three different MGD treatments. The study was conducted under the principles of the Declaration of Helsinki and was granted local ethical approval (NTY 08/07/070). Informed consent was provided by all participants prior to study commencement. Exclusion criteria included history or evidence of non-dry eye anterior segment disease, previous ocular surgery, trauma, or infection, current contact lens wear, and topical medications other than artificial tear supplements, which were avoided for 2 h prior to study participation.

A battery of baseline measures included non-invasive tear breakup time (NIBUT) measured with the aid of a Tearscope Plus™ with fine grid insert (timed from blink to observation of first distortion in the grid pattern, Keeler, Berkshire, UK), tear meniscus height (TMH) calculated from a calibrated digital image by a masked investigator, and lipid layer grade (LLG), evaluated by tear film interferometry [11] (Tearscope Plus; Keeler, UK) and graded as: 0 (absent), 1 (open meshwork), 2 (closed meshwork), 3 (wave), 4 (amorphous), or 5 (coloured fringes). Meibomian gland drop out was determined by infrared meibography [12,13] (SDZ Electronics, Auckland, NZ), and represents the area covered with glands, as a proportion of the full tarsal area expected to house glands [14]. Corneal temperature variation factor (TVF) was determined with an infrared thermographer (TVS-200, Applied Infrared Sensing, Australia) [15], and tear film evaporation rate was measured with a modified evaporimeter (EP-2, ServoMed, Sweden) [16]. Each participant was randomly allocated to receive one of three treatment modalities; latent heat device (Blephasteam, Spectrum-Théa, UK, $n = 25$), liposomal spray (TearsAgain®, Optima, Germany, $n = 28$), or Eyebag® (MGDRx®, Eyebag Company, UK, $n = 28$). Treatment was applied to both eyes in each case, by an unmasked clinician uninvolved in data collection for the study, to preserve investigator masking. McMonnies Dry Eye Questionnaire symptom scores were calculated before and after treatment.

The pre-heated latent heat device, containing saline-soaked ring inserts, was applied according to the manufacturer's instructions for a period of 10 min. Eyebags were heated, according to the manufacturer's guidelines, for 30 s at full power in a 900W microwave, shaken on removal to ensure even heat distribution, then applied immediately to the eyes of the participant, with the silk side adjacent to the eyelids, for a period of 10 min. Participants in the liposomal spray group received one full spray to each closed eye in turn. Once the treatment had been applied, participants were asked to remain seated, blinking normally, for the treatment period of 10-min.

Based on the percentage of meibomian gland (MG) dropout observed by infrared meibography, eligible participants were pooled into one of three groups: control ($\leq 5\%$ MG dropout), mild MG dropout (between 5 and 40%) or pronounced MG dropout ($\geq 40\%$). Retrospective severity classification ensured masking of the participants MG dropout classification to the researchers.

Ten minutes after the treatment period, the same battery of dry eye tests was repeated, and the results were pooled by treatment. The main outcome measures were the differences in pre- and post-treatment measures, which were compared across treatment groups and MG

dropout groups. Only data from right eyes were included in the analysis. Statistical testing was performed in SPSS (V22, IBM, USA). Equivalence of the three treatment groups at baseline was assessed with one-way ANOVA. Paired pre- and post-treatment results were compared with a general linear model for parametric variables, and with Wilcoxon and Kruskal–Wallis (KW) tests for comparisons over time and between groups, respectively, for non-parametric variables. Power calculations indicated that a minimum of 15 participants was required, per group, to detect a clinically significant difference (one lipid layer grade) for the inter-group comparisons at 80% power with an alpha of 0.05. Results were considered significant at $p < 0.05$.

3. Results

3.1. Severity classifications

Eighty-one participants completed the study, with 27 classified with mild gland dropout, 33 with pronounced dropout, and 21 controls. McMonnies Dry Eye Questionnaire symptom scores correlated with the percentage of MG dropout ($r = 0.618$, $n = 81$, $p < 0.001$), increasing with severity group ($F = 54.27$, $p < 0.001$, Table 1). At baseline, there was no difference between treatment groups for McMonnies Dry Eye Score ($F = 0.54$, $p = 0.585$), MG dropout percentage ($F = 0.71$, $p = 0.494$), or sex ($F = 0.24$, $p = 0.942$). Overall, MG dropout showed a positive correlation with age ($r = 0.541$, $p < 0.001$), but the mean ages of participants in each treatment group were not different ($F = 0.22$, $p = 0.801$).

3.2. Clinical measures

Prior to treatment, there was a significant difference in NIBUT between the 3 severity groups ($F = 21.66$, $p < 0.001$, Fig. 1), with the control group (7.14 \pm 2.54 s) exhibiting a longer NIBUT than both the mild (5.60 \pm 1.90s, $p = 0.015$) and pronounced MGD (3.80 \pm 1.17 s, $p < 0.001$) groups. Following treatment, there was an overall improvement in NIBUT ($F = 4.85$, $p = 0.010$), with no effect of treatment type ($F = 0.99$, $p = 0.131$). Post-hoc testing revealed that the improved NIBUT after treatment was significant only for the group with pronounced MGD (4.32 \pm 1.15 s, $p = 0.008$), with the mild and control groups failing to reach significance (mild: 6.17 \pm 2.22 s, $p = 0.057$, control: 6.47 \pm 2.06 s, $p = 0.172$). However, a result of this improvement meant that there was no longer a significant difference between the NIBUT of the control and mild MGD groups ($p = 0.843$) following treatment.

At baseline, the lipid layer grade (LLG) was different between MG dropout groups ($\chi^2 = 41.97$, $p < 0.001$), with the control group LLG (Median: 4 (IQR: 2.0–4.0)) higher than both the mild (Median: 2 (IQR: 1.0–2.0), $p < 0.001$) and pronounced (Median: 1.5 (IQR: 0.0–2.0), $p < 0.001$) groups, which were not different from each other ($p = 0.373$). Following treatment, there was an overall improvement in LLG ($\chi^2 = 40$, $p = 0.009$), but again, no effect of treatment type ($p = 0.349$). Post hoc testing revealed a significant difference in the improvement in LLG between the three MGD severity groups ($p < 0.001$) with the mild group LLG increasing from 2.0 (IQR: 1.0–2.0) to 3.0 (IQR: 2.0–3.0, $\chi^2 = 20$, $p < 0.001$), and the

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