Thermal Pulsation with or without Dexamethasone Intracanalicular Insert for Meibomian Gland Dysfunction: A Prospective, Masked Trial

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Significance: Meibomian gland dysfunction (MGD) is among the most common causes of dry eye disease worldwide. Few studies have compared treatment options, and the basis for an evidentiary approach to MGD management is lacking. We have conducted a non-randomized trial evaluating the additive benefit of a recently developed therapy.

Purpose: To compare the efficacy of thermal pulsation therapy alone or combined with the dexamethasone intracanalicular insert (Dextenza) on the signs and symptoms of MGD.

Methods: This was a prospective, patient-masked, sham-controlled, non-randomized trial. All subjects underwent thermal pulsation therapy using the LipiFlow system. The dexamethasone intracanalicular insert was placed in the inferior canaliculus of the more symptomatic eye (DEX group), while sham punctal dilation of the fellow eye was performed to preserve patient masking (SHAM group). Key outcomes were improvement in meibum expressibility at 1, 4, and 12 weeks and patient treatment preference at week 12.

Results: Nineteen subjects underwent thermal pulsation therapy and received the DEX insert. Meibomian gland expressibility scores improved significantly in both groups at 1, 4, and 12 weeks, with significantly greater improvement in DEX eyes than SHAM eyes at 12 weeks (P=0.027). Improvement from baseline in TBUT was significant at all time points in DEX eyes and only at week 4 in SHAM eyes, with significantly greater improvement in DEX eyes over SHAM eyes at week 12 (P=0.028). Mean best-corrected visual acuity and intraocular pressure remained unchanged from baseline throughout follow-up in both groups, and no adverse events were noted. Combined therapy with DEX was preferred by 61% of subjects.

Conclusion: This study demonstrated a significant benefit of combining thermal pulsation therapy with the dexamethasone intracanalicular insert on signs of MGD including TBUT and meibomian gland expressibility score. Consequently, a majority of patients preferred combination therapy to thermal pulsation therapy alone.

Keywords: Dextenza, dexamethasone, LipiFlow, thermal pulsation therapy, meibomian gland dysfunction

Introduction

Meibomian gland dysfunction (MGD) is defined by the Tear Film and Ocular Surface Society (TFOS) as

a chronic, diffuse abnormality of the meibomian glands, commonly characterized by terminal duct obstruction and/or qualitative/quantitative changes in the glandular secretion … [that] may result in alteration of the tear film, symptoms of eye irritation, clinically apparent inflammation, and ocular surface disease

and may be the leading cause of dry eye disease throughout the world. Its prevalence ranges from ~4–20% in Caucasian populations and may affect more than 60% of some Asian populations.

Due to a paucity of well-designed and appropriately powered clinical studies, the clinical approach to MGD is neither standardized nor evidence-based. Lid hygiene, coupled with lid warming and compression, are commonly recommended, but instructions by providers and techniques employed by patients vary significantly. Antibiotics with or without steroids are also commonly prescribed, with a meta-analysis demonstrating the benefits of topical azithromycin on short-term
improvement of tear film quality\textsuperscript{2} and several studies demonstrating improvements in tear film inflammatory mediators, gland expressibility, and/or clinical symptoms with the use of topical corticosteroids.\textsuperscript{3–5}

Integrated systems utilizing a combination of heat and directed pressure on the eyelids to facilitate expression of meibum from inspissated or blocked meibomian glands have been developed and commercialized for the treatment of MGD.\textsuperscript{6} One such system (LipiFlow, Johnson & Johnson) is designed to warm the lid to soften and liquify meibum and compress the lid with a series of peristaltic proximal-to-distal pulses to express liquified meibum from dysfunctional glands. In its pivotal trial and subsequent studies, this therapy significantly improved both meibomian gland function and clinical symptoms of ocular surface disease.\textsuperscript{6–10}

We have conducted a prospective subject-masked trial to compare the effects of thermal pulsation therapy with the LipiFlow system with or without the dexamethasone intracanalicular insert (Dextenza, Ocular Therapeutix) on the signs and symptoms of MGD. The insert is a rod-shaped hydrogel matrix incorporating 0.4 mg preservative-free dexamethasone, is placed in the canalculus, and provides sustained-release delivery of dexamethasone to the ocular surface for 30 days.\textsuperscript{11–13} It is currently approved in the United States for the control of postoperative pain and inflammation following ocular surgery.\textsuperscript{14}

**Methods**

This was a single-center, open-label, prospective, non-randomized, subject-masked, sham-controlled trial. The protocol was reviewed and approved by the Western IRB on 7/2/2020. The study was registered at ClinicalTrials.gov (NCT04413279) on 6/2/2020. Participants were enrolled between 8/5/2020 and 4/14/2021; all participants provided written informed consent. The study was conducted in accordance with the tenets of the Declaration of Helsinki.\textsuperscript{15}

Eligible subjects were adults aged 18 years or older with history of evaporative dry eye disease, meibomian gland dysfunction, and clinically significant inflammation as evidenced by ocular surface staining and/or conjunctival hyperemia and/or elevated MMP-9 levels. Exclusion criteria included ocular or nonocular infection, compromised nasolacrimal flow, or concurrent use of or contraindications to corticosteroids. Consecutive eligible subjects were invited to participate in the study.

All subjects underwent a clinical evaluation to establish eligibility consisting of uncorrected and best-corrected visual acuity (UCVA and BCVA), meibomian gland assessment, tear film osmolarity (TearLab) and matrix metalloproteinase 9 (MMP-9; Inflammadry, Quidel) assessment, corneal fluorescein and conjunctival lissamine green staining, tear break-up time (TBUT), intraocular pressure (IOP), and a dilated eye examination. Meibomian gland assessment mirrored the methodology in the pivotal LipiFlow trial\textsuperscript{10} and consisted of grading the quality of meibum expression from 15 glands along the lower eyelid, 5 each from the temporal, central, and nasal regions, and each graded on a 0–3 scale as follows: 3, clear liquid secretions; 2, cloudy liquid secretions; 1, inspissated/toothpaste consistency; and 0, no secretions. A composite meibomian gland expressibility score ranging from 0 to 45 (with lower scores representing worse disease) was tabulated by summing the grades of all 15 glands assessed. Corneal fluorescein staining was graded from 0 to 3 (none to heavy staining) in five regions (superior, inferior, nasal, temporal, and central) and summed for a corneal staining score. Conjunctival lissamine green staining was graded on the same 0–3 scale in 6 regions (3 nasal and 3 temporal) and summed for a conjunctival staining score. Corneal and conjunctival scores were summed to produce an overall ocular surface staining score. Subjects also completed the validated DEQ-5 Dry Eye Questionnaire, which characterizes the presence and severity of ocular discomfort, dryness, and watering; possible scores range from 0 to 22 with higher scores representing worse symptoms.\textsuperscript{16}

Qualifying subjects underwent bilateral thermal pulsation therapy with the LipiFlow system 1–30 days later. The procedure has been described in detail previously\textsuperscript{8–10} and was performed in accordance with the manufacturer’s directions. Briefly, under topical anesthesia, the activator was placed on the eye such that the corneal shield rested on the ocular surface (vaulting the cornea to protect it from heat) and the inflatable bladder rested on the lid surface. Over a 12-minute treatment period, the lids were gently heated and expressed with repeated vectored pressure pulses. Following the procedure, the DEX insert was placed in the inferior canalculus of the more symptomatic eye (the DEX group), and the inferior punctum of the fellow eye was dilated using a punctal dilator to mimic insert placement to achieve patient masking to treatment (the SHAM group). No anti-inflammatory therapy was applied to the SHAM eye.
During the study, although patients were permitted to continue warm compresses and lid scrubs in either or both eyes at their discretion, and to continue habitual dry eye treatments such as topical immunomodulators and/or oral omega fatty acid supplements. Subjects were re-evaluated 1, 4, and 12 weeks later, at which time all assessments listed above were repeated and safety assessed. Additionally at week 12, subjects completed the validated Comparisons of Ophthalmic Medications for Tolerability (COMTOL) questionnaire adapted for the treatments utilized in this study.

The first key outcome measure of this study was the change from baseline in meibomian gland expressibility scores at weeks 1, 4, and 12 and was compared between treatment groups using paired t-tests as between-group data were drawn from correlated fellow-eye pairs. The second key outcome measure was patient preference for therapy as measured by the COMTOL instrument at week 12. Secondary outcomes included mean changes in BCVA, tear film osmolarity, MMP-9 positivity rates, ocular surface staining scores, TBUT, and DEQ-5 scores from baseline to weeks 1, 4, and 12; these were also analyzed using paired t-tests except for the dichotomous MMP-9 parameter for which the Fisher Exact Test was utilized. Safety outcomes included the nature and incidence of adverse events. No formal power analysis was conducted a priori; rather, a convenience sample consistent with recent prior studies of similar design and purpose (40 eyes of 20 subjects) was selected.

Results

Overall, 20 subjects were enrolled. No patients had previously undergone microblepharoexfoliation, thermal pulsation, or intense pulsed light therapy in the past 12 months. Their mean (standard deviation) age was 59.2 (11.1) years, 18/20 (90%) were female, and 19/20 (95%) identified themselves as white. DEX insertion was not possible in 1 subject who was excluded from all outcomes analyses; all other subjects completed the trial.

Mean meibomian gland expressibility scores and other outcomes data at each time point are given in Table 1. In DEX-treated eyes, significant improvements from baseline were seen in meibomian gland expressibility scores at post-treatment time points \( P<0.0001 \), ocular surface staining scores at 1 \( P=0.035 \) and 4 weeks \( P<0.001 \), and TBUT at all time points \( P<0.037 \). In SHAM-treated eyes, significant improvements from baseline were seen in expressibility scores at all time points \( P<0.0001 \) and TBUT at week 4 \( P=0.020 \). Significantly greater improvements were seen in DEX eyes compared to SHAM eyes for expressibility scores at 12 weeks \( P=0.027 \), ocular surface staining score at 4 weeks \( P=0.028 \), and TBUT at 12 weeks \( P=0.028 \). In both treatment groups, the rate of MMP-9 positivity decreased by 16–46% across all visits; these were not significant changes within or between groups. Significantly greater improvements in SHAM eyes compared to DEX eyes were not seen for any parameters at any time point.

Symptom scores on the DEQ-5 improved from baseline at each post-treatment visit. Mean DEQ-5 scores were 12.3 (4.4) at baseline, 11.1 (4.7) at week 1 \( P=0.132 \), 10.3 (5.1) at week 4 \( P=0.078 \), and 9.1 (5.9) at week 12 \( P=0.019 \). The DEQ-5 is an individual-level and not eye-level instrument and cannot assess differences between eyes. The COMTOL instrument, however, is designed to compare treatment experiences in subjects exposed to both treatments. Of the 18 subjects reporting a treatment preference using the COMTOL instrument, 11 (61.1%) preferred LipiFlow with DEX and 7 (38.9%) preferred LipiFlow with SHAM. One subject reported no preference between treatments.

Both the thermal pulsation therapy and the DEX insert were safe and well tolerated in this sample. No adverse events were noted in either group. Mean BCVA and IOP remained stable throughout follow-up (Table 2). No patients had an IOP rise >10 mmHg; a single patient had an 8-mm IOP rise in the eye receiving DEX from 15 mmHg at baseline to 23 mmHg at week 4 that resolved without intervention.

Discussion

In this prospective, sham-controlled, non-randomized study, thermal pulsation therapy + DEX provided significantly greater improvement in meibomian gland expressibility and TBUT at 12 weeks and in ocular surface staining at 4 weeks compared to thermal pulsation therapy + SHAM. The majority (61%) of patients undergoing thermal pulsation lid therapy for symptomatic MGD preferred combined therapy with the DEX insert over sham therapy (39%). The interventions assessed in this study were safe and well tolerated by all study participants.

The therapeutic benefits of thermal pulsation lid therapy on symptomatic MGD have been thoroughly characterized in the literature, and a meta-analysis demonstrated its superiority over warm compress treatment for treating dry eye.
<table>
<thead>
<tr>
<th>Table 1</th>
<th>Meibomian Gland Expressibility Scores and Other Endpoint Data by Treatment Group and Time Point</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
</tr>
<tr>
<td></td>
<td>DEX</td>
</tr>
<tr>
<td>Meibomian gland expressibility score</td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>13.3 (8.1)</td>
</tr>
<tr>
<td>P value</td>
<td>0.182</td>
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<tr>
<td>Mean (SD) CFB</td>
<td>–</td>
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<tr>
<td>P value (within-group CFB)</td>
<td>–</td>
</tr>
<tr>
<td>P value (between-group CFB)</td>
<td>–</td>
</tr>
<tr>
<td>Tear osmolarity (mOsm/L)</td>
<td></td>
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<tr>
<td>Mean (SD)</td>
<td>305 (8.8)</td>
</tr>
<tr>
<td>P value</td>
<td>0.122</td>
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<tr>
<td>Mean (SD) CFB</td>
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<tr>
<td>P value (within-group CFB)</td>
<td>–</td>
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<tr>
<td>P value (between-group CFB)</td>
<td>–</td>
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<tr>
<td>Positive MMP-9</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>16 (84)</td>
</tr>
<tr>
<td>P value</td>
<td>0.999</td>
</tr>
<tr>
<td>No. (%) CFB</td>
<td>–</td>
</tr>
<tr>
<td>P value (within-group CFB)</td>
<td>–</td>
</tr>
<tr>
<td>P value (between-group CFB)</td>
<td>–</td>
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<tr>
<td>Ocular surface staining score</td>
<td>Mean (SD)</td>
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<td>------------------------------</td>
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<td></td>
<td>( P ) value</td>
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<tr>
<td>Mean (SD) CFB</td>
<td>–</td>
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<tr>
<td>( P ) value (within-group CFB)</td>
<td>–</td>
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<tr>
<td>( P ) value (between-group CFB)</td>
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| TBUT                        | Mean (SD) | 3.2 (2.2) | 4.1 (3.4) | 4.9 (4.6) | 4.6 (3.3) | 6.3 (5.8) | 6.1 (5.5) | 6.1 (4.8) | 4.7 (3.4) |
|                            | \( P \) value | 0.212 | 0.705 | 0.731 | 0.125 | 0.037 | 0.318 | 0.006 | 0.020 | 0.002 | 0.429 |
|                              | Mean (SD) CFB | –         | –         | 1.7 (3.3) | 0.5 (2.2) | 3.1 (4.4) | 2.0 (3.5) | 2.9 (3.3) | 0.6 (3.3) | –         | –         | –         | –         | –         | –         | –         | –         | –         |
| \( P \) value (within-group CFB) | –         | –         | 0.037 | 0.318 | 0.006 | 0.020 | 0.002 | 0.429 | –         | –         | –         | –         | –         | –         | –         | –         | –         | –         |
| \( P \) value (between-group CFB) | –         | 0.139 | 0.256 | 0.028 | –         | –         | –         | –         | –         | –         | –         | –         | –         | –         | –         | –         | –         | –         |

**Abbreviations:** MMP-9, matrix metalloproteinase-9; SD, standard deviation; TBUT, tear break-up time.
The benefit of corticosteroid therapy for MGD is less well characterized. In general, brief therapy with steroids are beneficial in the setting of acute inflammatory flares of ocular surface disease, while the long-term side effects of steroids—including elevated IOP and cataract formation—preclude their chronic use. The DEX insert is a formulation of dexamethasone designed for sustained-release drug delivery over a 30-day period. It is approved in the United States for the control of pain and inflammation following ocular surgery, and its role in postoperative care has been demonstrated following cataract extraction in adults and children, as well as refractive surgical procedures. Phase 2 and 3 trials have also evaluated DEX for chronic inflammation associated with allergic conjunctivitis and reported short-term improvements in itching and conjunctival hyperemia. Given the role of inflammation in MGD, we hypothesized in this study that DEX may provide additional therapeutic benefit when combined with thermal pulsation therapy for MGD. The DEX insert has several features to support this hypothesis. First, it provides short-term pulsed therapy with a diminishing dose over time to minimize complications related to IOP and cataract formation and with minimal systemic absorption. Second, it is preservative-free, which is important given the pro-inflammatory nature of preservatives in ophthalmic formulations and their adverse effects on ocular surface disease. Third, its anti-inflammatory mechanism of action is complementary to that of thermal pulsation therapy, favoring additivity of efficacy.

In this study, both treatment groups demonstrated significant improvements in meibomian gland expressibility, but the improvement was significantly greater in eyes treated with thermal pulsation therapy + DEX. Similarly, TBUT was significantly improved in the DEX (but not the SHAM) group at 12 weeks, and ocular surface staining was improved in the DEX (but not the SHAM) group at week 4. All of the significant between-group differences favored combination therapy with DEX. This was an expected outcome of the study, as prior studies supported the benefits of corticosteroid therapy for MGD. Thus it is likely that patient preference favored combination therapy given the better outcomes in this group.

Strengths of this study include its prospective nature as well as the use of sham therapy for subject masking. Limitations include both a relatively small sample size and a short study duration given the chronic nature of MGD.

In summary, we have demonstrated a significant benefit of combining thermal pulsation therapy with the dexamethasone intracanalicular insert on signs of MGD including TBUT and meibomian gland expressibility score. Consequently, the majority of patients preferred combination therapy to thermal pulsation therapy alone.

Data Sharing Statement
The investigators will consider reasonable requests for sharing of the de-identified data set upon request to the corresponding author.

Funding
Sponsorship for this study was provided by Ocular Therapeutix.

Disclosure
Dr Damon S Dierker reports grants and personal fees from Ocular Therapeutix, during the conduct of the study; personal fees from Aerie, Alcon, Allergan, Azura, Bio-Tissue, Eyevance, Johnson & Johnson, Kala Pharmaceuticals, Lumenis,
Novartis, Oyster Point Pharma, Quidel, ScienceBased Health, Scope, Sight Sciences, Sun Pharma, Tarsus, TearLab, and Thea Pharmaceuticals, outside the submitted work. Dr Scott G Hauswirth reports personal fees from Ocular Therapeutix, during the conduct of the study; personal fees from Dompé, Kala Pharmaceuticals, Sun Pharmaceuticals, Takeda, Oyster Point, Sight Sciences, Horizon Pharmaceuticals, and NuSight Medical; non-financial support from TearRestore and Science Based Health for advisory work, outside the submitted work. The authors report no other conflicts of interest in this work.

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