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TREATMENT FOR CONJUNCTIVOCHALASIS: A COMBINED APPROACH UTILIZING RADIOFREQUENCY CAUTERIZATION AND THERMALID™ PROCEDURE

Liem H. Nguyen[1], BS, Edward H. Jaccoma, MD

[1]University of New England College of Osteopathic Medicine, Biddeford, ME

Correspondence may be directed to: ejaccoma@aol.com

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ABSTRACT

Background

Dry Eye Disease (DED) and related ocular surface diseases have multiple etiologies, but two of the most prevalent are Meibomian Gland Dysfunction (MGD) and Conjunctivochalasis (CCH). This study examines a customizable two-step approach utilizing radiofrequency to treat these two commonly coexisting conditions and provide patients with relief from DED signs and symptoms.

Study Design

An IRB approved retrospective chart review of 25 consecutively treated patients was conducted. Patients were included if they presented with DED symptoms and were treated with a combination treatment approach to improve both MGD and CCH, with pre- and post-treatment dry eye metrics outlined below. Follow-up visit information was compared to pre-treatment baseline to evaluate the efficacy and safety of treatment.

Results

Statistically significant results were observed in a decrease in symptoms as evaluated by the primary endpoints of the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire and an increase in the number of Meibomian Glands Yielding Liquid Secretion (MGYLS). Tear Meniscus Height also saw statistically significant improvement while Non-invasive Tear Break-Up Time (NTBUT) and Schirmer's saw minor progress. Clinical evaluation and ocular surface photographs showed marked improvement in CCH with minimal observed side effects during post-operative follow-up visits.

Conclusion

A two-step approach utilizing a radiofrequency device to treat dry eye symptoms provides significant clinical improvement and symptomatic relief for a broad spectrum of patients who had received a variety of prior treatments for DED.

INTRODUCTION

Conjunctivochalasis (CCH) is an ocular disorder described as a nonedematous, loose, and redundant conjunctiva, most commonly affecting the inferior bulbar conjunctiva that situates between the lower eyelid and the globe.[1] The condition can affect all parts of the inferior bulbar area, including the nasal, central, or temporal portions. It usually occurs bilaterally, and its prevalence increases with age.[2,3–6] According to Mimura et al., in his hospital-based study of 1,416 patients, the prevalence of conjunctivochalasis increased dramatically with age (one to 10 years, 6.8%; 11 to 20 years, 36.2%; 21 to 30 years, 61.5%; 31 to 40 years, 71.4%; 41 to 50 years, 90.2%; 51 to 60 years, 94.2%;

61 to 70 years, 98.0%; 71 to 80 years, 99.0%; 81 to 90 years, 98.5%; and 91 to 100 years, 100.0%).[6]

Conjunctivochalasis' pathogenesis, though there is no consensus, roots in the loss of conjunctival epithelial cohesiveness and increased collagenolytic activity due to an inflammatory pathway that may, at least in part, relate to increased friction from poor tear lubrication.[2,3,7–9] It relates to other ophthalmic conditions such as ocular irritation, pterygium, dryness, subconjunctival hemorrhage, and blurred vision.[7,8] A recent study has shown a decrease in Tear Break-Up Time (TBUT) and delayed tear clearance in patients with significant conjunctivochalasis.[9,10] The redundant conjunctiva can impact the tear meniscus's normal function along the lid margin, leading to a reduction in tear volume of the inferior fornix, which serves as a reservoir. This affects the even delivery of tears to the ocular surface. The disruption of structure results in the impairment of conjunctival function, leading to tear-film thinning and instability.[11–13]

A recent report by Pflugfelder et al. noted that Tear Meniscus Height was elevated in eyes with CCH due to redundant conjunctiva protruding into the inferior fornix. This has the effect of pushing the tear meniscus anteriorly over the lid margin while diminishing the inferior fornix's reservoir capacity. Tear anterior migration, coupled with the elevated osmolarity and inflammatory mediators common to CCH and DED, can lead to changes in the lid margin and MG orifices observed as increased degrees of Marx's line, which is associated with worsening of DED. They also pointed to the importance of identifying and treating CCH before these structural changes occur.[14]

Meibomian gland dysfunction (MGD) is one major cause of DED.[15] Meibomian glands are holocrine, sebaceous glands that secrete meibum, a lipid consists of cholesterol, triacylglycerol, free fatty acids, wax ester, and phospholipids. This secretion serves as a coat to stabilize the tear-film by retarding evaporation. Therefore, dysfunction of these glands leads to a decrease in TBUT, causing the typical dry eye symptoms, including redness, irritation, and sandy sensations that patients with DED experience and frequently report.[4,5]

Thermal pulsation treatment is the leading predicate treatment for reducing the obstructions shown to result in most MGD cases. A recent study has shown the benefits of utilizing radiofrequency to melt and express these obstructions and improve dry eye signs and symptoms associated with obstructive MGD.[16]

It seems apparent that obstructive MGD would be a leading cause of CCH as the lack of lubrication from these oil glands leads to an increase in friction from each blink, thus exacerbating the condition. Lack of oil also increases evaporation, which subsequently increases tear osmolarity and inflammation, leading to additional CCH through the breakdown of more collagen. The worsening of CCH will negatively affect the tear-film and tear distribution, which will worsen DED and result in more severe and refractory dry eye symptoms. Treatment of CCH should improve DED by recovering the tear meniscus function and reestablishing the inferior fornix volume and reservoir functionality. At the same time, treating MGD could help fix the root cause of CCH.

There are many non-surgical methods, including topical lubricants in eye drops, ointments, and topical corticosteroids to manage CCH. These treatments can improve tear-film stability and lessen the mechanical friction from each blink that could worsen the redundant conjunctiva. However, such benefits are typically transient, while surgical treatments, such as conjunctival cauterization or conjunctival excision with or without graft or scleral fixation of the conjunctiva, can each provide definitive treatment for CCH.[17]

Electrosurgical radiofrequency (RF) systems, which made their debut in 1928, are now widely utilized to treat conjunctivochalasis by providing a definitive cauterization of the redundant conjunctival folds. This treatment has been shown to improve symptoms of CCH by causing physical damage to the tissue, leading to subsequent shrinkage and flattening of the redundant conjunctiva.[16–22] However, its effectiveness in a combination treatment to target dry eye disease (DED) caused by MGD has not received much attention.

MATERIALS AND METHODS

Treatment Device Description/Study Design

This is an IRB approved retrospective chart review of 25 consecutively treated patients. Patients were included if they presented with chronic and refractive DED symptoms, including the sensation of dryness, burning, irritation, redness, impairment of visual acuity,

persistent chalazia, who were diagnosed with concurrent CCH and had both the pre- and post-treatment dry eye metrics from the ocular examination. All patients involved in the study had utilized prior traditional and less traditional front-line treatments, such as Blephex, Lipiflow, Restasis, Xiidra, and eyelid (ThermaLid) radiofrequency therapy, without significant clinical improvements of symptoms. Almost all patients were on a daily regimen of artificial tears, oral oil supplements, and lid hygiene (Hypochlorous acid spray, terpinol lid wipes, warm compresses, microwavable eyelid mask), all of which only yielded brief symptomatic or incomplete relief (Figure 1).

Initial grading of CCH utilizes the Lid-Parallel Conjunctival Folds (LIPCOF) system described by Hoh but modified according to the following: LIPCOF grade 0 indicates the lack of the conjunctival folds; LIPCOF grade 1 means there was only one conjunctival fold upon examination; LIPCOF grade 2 illustrates multiple conjunctival folds that do not extend the tear meniscus upon examination; LIPCOF grade 3 represents multiple conjunctival folds that extend the tear meniscus upon examination; a grade 4, which signifies a fold hanging over the margin of the lid upon examination, was added to the grading system as these patients are blinking on their conjunctiva, so that stronger blinking results on additional trauma and discomfort. The LIPCOF grading has been shown to correlate with the dry eye symptoms reported subjectively by patients (Table 1).[23,24]

These patients underwent a combination treatment that includes cauterization and thermal lid expression (ThermaLid) therapy by utilizing the single 4MHz Monopolar Radiofrequency (RF) Pellevé S5 generator system to target both MGD and CCH.[16–21,25]

The topical anesthetic administration was followed by local subconjunctival injection of approximately 0.2 cc 1% lidocaine with 1: 100,000 epinephrine to the treatment eye. Placement of a neutral plate on the patient's back, between the shoulders, ensured full contact of the plate with the patient's skin. The physician then instructed the patient to up-gaze at the slit lamp while the lower lid was manually retracted to expose the lower bulbar CCH.

Treating CCH utilized the CUT mode with usage of smooth, angled MacPherson forceps to grasp the redundant tissue and a 2mm ball tip electrode to apply energy to the fornix folds on a power setting of 4. Post

FIG. 1 Pre-study treatments data. Data showed significant interventions for DED from the majority of patients before the study.

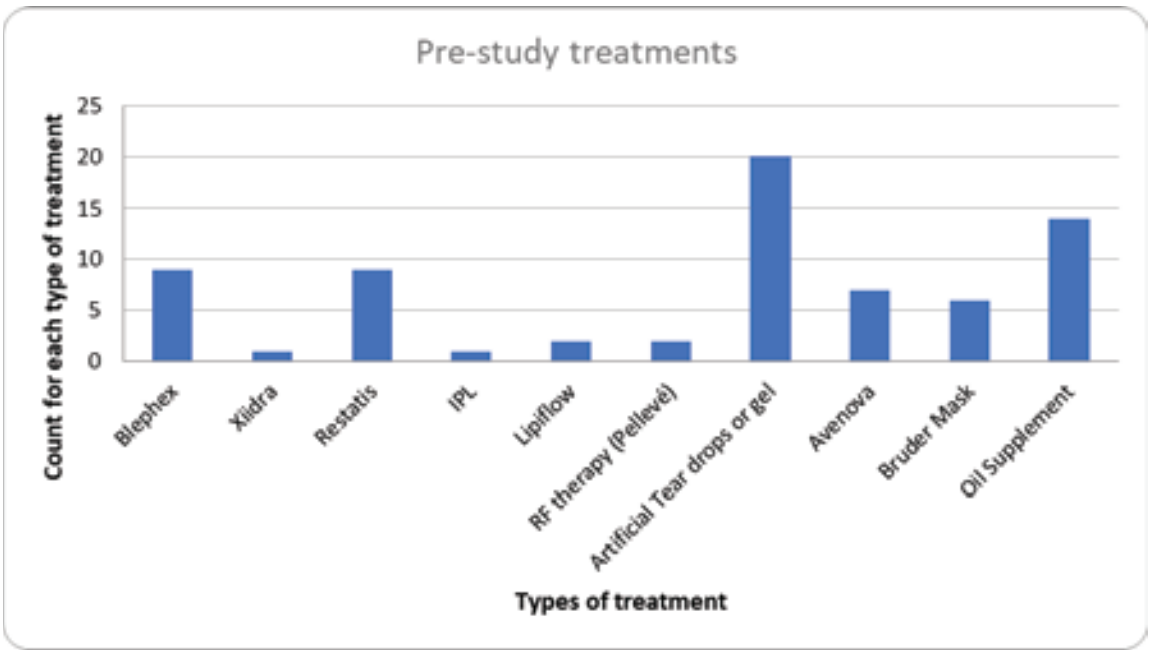

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TABLE 1 Comparison between Average Pre-and Post-treatment LIPCOF CCH Grading

Subject	CCH Grading Baseline		CCH Grading Follow-up	
	OD (R)	OS (L)	OD (R)	OS (L)
1	2.5	2.5	0.5	0.5
2	2	2	0	0
3	3	3	0	0
4	2.5	2.5	0.5	0.5
5	2.5	2.5	1.5	0
6	3.5	3.5	0.5	0.5
7	3	3	1	0
8	2	2	0	0
9	2.5	2.5	0	0
10	NA	2.5	NA	0
11	2.5	2.5	0	0
12	3	3	0.5	0
13	2.5	2.5	0	0
14	2	2	1.5	1.5
15	1.5	1.5	0	0
16	1.5	1.5	0	0
17	1.5	1.5	0	0
18	2.5	2.5	2	2
19	2	2.5	0	0
20	2	2	1	NA
21	1.5	1.5	0	0
22	3	2	0	0
23	2	1.5	0	0
24	2	2	0	0
25	1.5	1.5	0	0
Average	2.27	2.24	0.38	0.21

anesthetic treatment time per eye was approximately 3-5 minutes.

After CCH plication, a ThermaLid treatment of obstructive MGD was described in detail and referred to as the "ThermaLid treatment," in the previous publication: MGD-Related Dry Eye Treatment Study: The ThermaLid™ Procedure, was then performed.[18] The sole deviation from that protocol was using a flexible, handled, rigid plastic corneal eye shield to cover the cornea (a ThermaShield ™) (Figure 2).

After treatments, each patient underwent a tapered course of a combination of Tobramycin and Dexamethasone ophthalmic drops with a scheduled follow-up within 1 week. If needed, the fellow eye's treatment happened about 4-6 weeks later, allowing full recovery from the initial treatment. The final follow-up was 4-6 weeks after completion

FIG. 2 Image of RF Treatment Procedure for MGD

of treatment of one or both eyes, at which symptoms were evaluated, and a dry eye exam was performed Figure 3 and Figure 4).

Follow-up visit information was compared to the baseline to evaluate the efficacy and safety of the treatment.[16] Subjective symptom measurements included the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire (a validated questionnaire, used to understand a patient's experience with symptoms common to Dry Eye, wherein scores range from zero to twenty-eight, with higher scores representing more frequent and severe symptoms). Objective measurements included Meibomian Glands Yielding Liquid Secretion (MGYLS), a measurement of the volume of liquid secretion of the gland described as zero, minimal, moderate, or copious. The integrity of the Meibomian glands, pre-treatment, and post-treatment, were evaluated to estimate the number of functional glands per each of 3 segments of the lid (nasal, central, and lateral) the Korb-MGE device. The Korb-MGE device serves as a "plunger" exerting a standard force of 1.25 g/mm^2 to the lid over an area of approximately 40 mm^2. This force approximates the forces applied by the lids to each other during forceful blinking. The amount of excretions provided by each region of Meibomian glands were visually evaluated and graded on a scale of zero (non-functional), scant (or minimal), moderate or copious as described by Korb and Blackie.[26]

Additional objective measurements included the Non-invasive Tear Break-Up Time (NTBUT) by an Oculus Keratograph (Figure 5), a measurement of

FIG. 3 Fluorescent stain imaging. Fluorescent stain of before (OD [top left], OS [bottom left]) and after (OD [top right] and OS [bottom right]) conjunctival plication treatment. Conjunctivochalasis is bilaterally improved with decrease in inferior bulbar conjunctival folds.

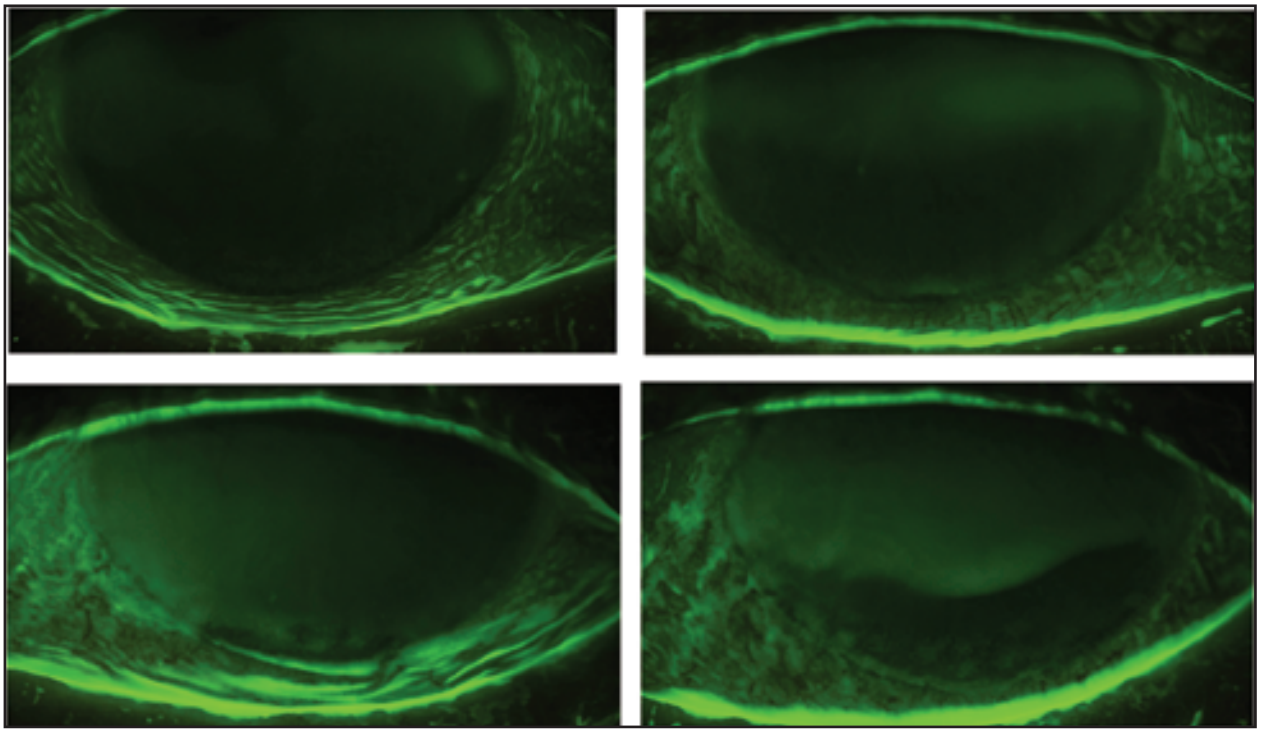

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FIG. 4 Tear-distribution imaging. Imaging of the eyes before (OD [top left], OS [bottom left]) and after (OD [top right] and OS [bottom right]) conjunctival plication treatment. Tear distribution improved bilaterally with better distribution across both eyes with a significant decrease in tear-film volume along the lower eyelid.

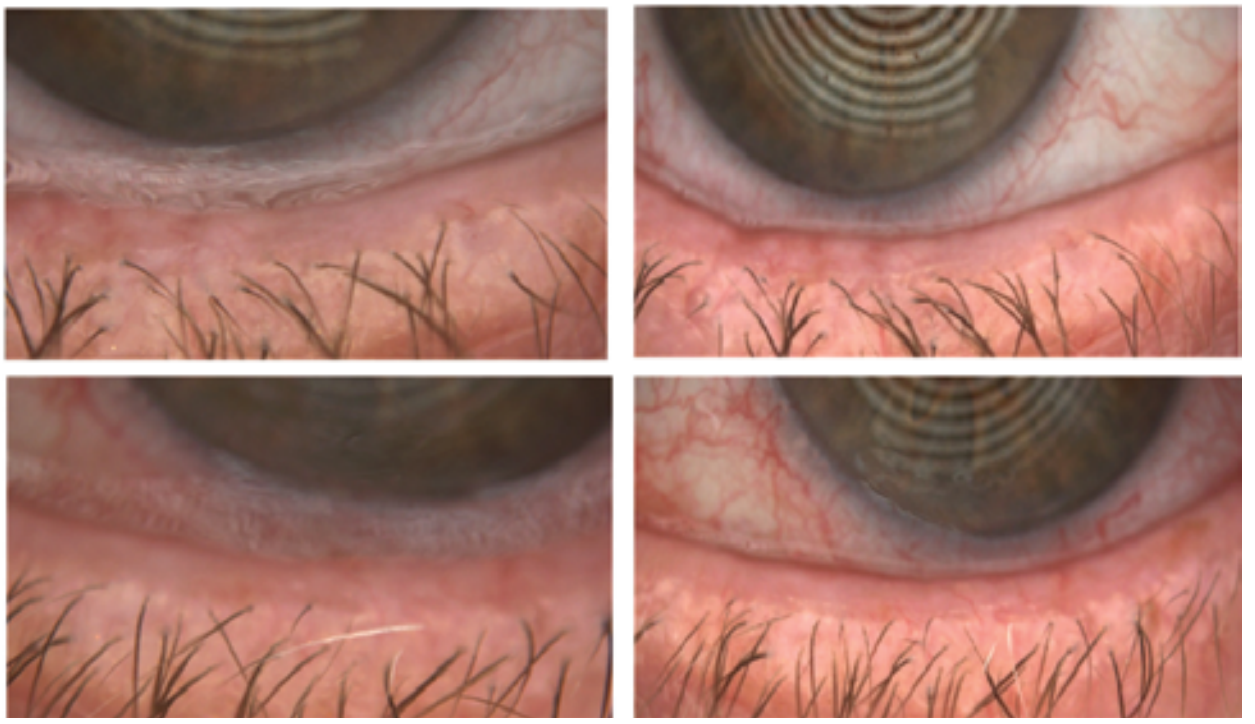
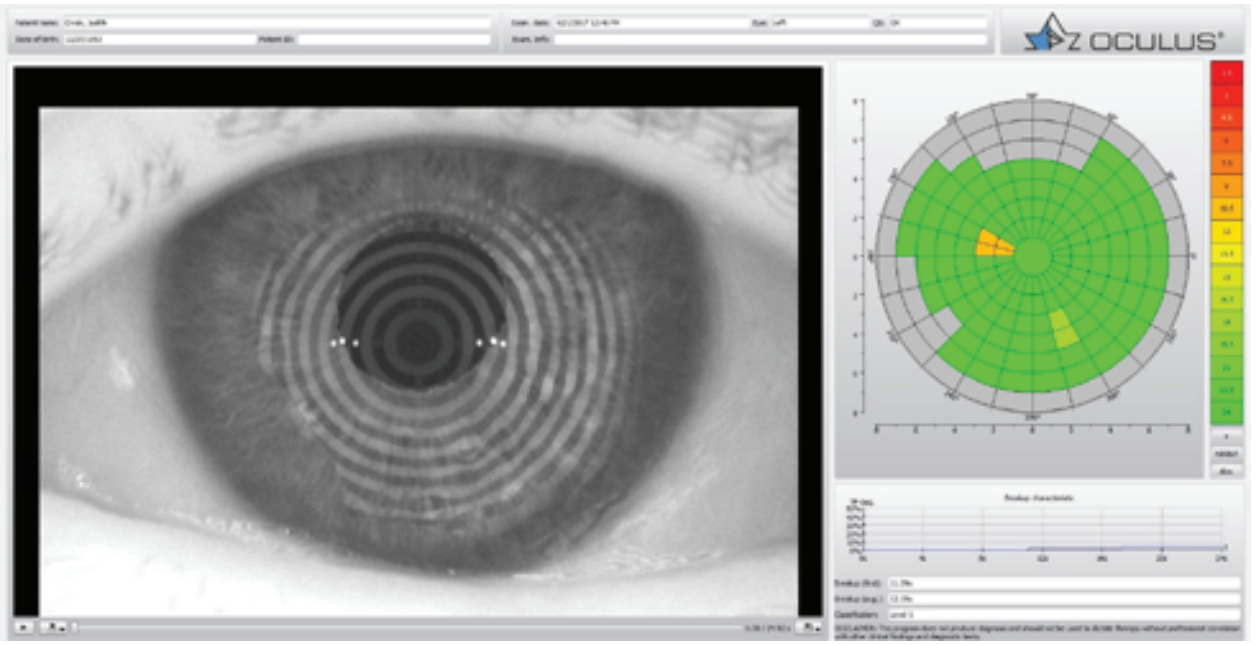


FIG. 5 NTBUT imaging shows a study patient's NTBUT. Normal value of initial NTBUT is greater than or equal to 10 seconds.



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tear-film stability, and Schirmer's testing with topical anesthetic, which utilizes Schirmer's Litmus paper to assess aqueous tear deficiency. Tear Meniscus levels and ocular surface and Meibomian gland photographs were also collected and compared during initial and post-procedural follow-up visits. A short video demonstrating Tempsure Treatment CCH with Thermalid can be seen here.

Subjects, post de-identification, got assigned a numerical identification code. All experimental procedures acquired approval by the New England Review Board (IRB) (Protocol # 120170291)

Statistical Analysis

The combined treatment's effectiveness was analyzed using a Two-Tailed Student's Paired t-test and Fisher's Exact Test where appropriate.

RESULTS

All patients in our patient population completed a bilateral treatment regimen. SPEED total decreased by 33.5% (p=0.001), and subject responses indicated that 80% of the subjects noted improvement (Table 2). The average total number of MGYLS producing moderate or copious amounts of tear oil increased from 24% at baseline to 47% at follow-up (p<0.001). Evaluation of Meibomian glands, using the Korb-MGE device, showed 23% of Meibomian glands, which were not working pre-treatment (glands that only yielded zero to minimum secretion), yielded significant liquid oil production. (Figure 6) Tear Meniscus Height improved by 36.6% compared to baseline (p<0.001). Non-invasive Tear Break-Up Time. (NTBUT) increased by 12.4% post-treatment (p=0.177). Schirmer's test results also increased by 12.2% (p=0.178) (Table 3).

Evaluation of photographs showed marked improvement in CCH (see Table 1 and Figures 2 and 3). Common side effects were tenderness and ocular irritation, which subsided within 2-5 days, and redness, which receded within 2 to 4 weeks. This is consistent with other studies that utilize a similar radiofrequency plication method on other patient populations.[17–21,25]

TABLE 2 Change of SPEED Score for Each Subject When Compared with Pre-treatment versus Post-treatment Data

Subject	SPEED Change
1	−1
2	−1
3	−20
4	2
5	8
6	−5
7	−3
8	1
9	−6
10	−4
11	3
12	−4
13	−3
14	−4
15	−16
16	−16
17	−13
18	−8
19	−4
20	−13
21	−4
22	−1.5*
23	−11
24	NA
25	−2

** patient response was in between two numbers during post-treatment evaluation*

DISCUSSION

CCH, along with MGD, is one of the major causes of chronic DED since it disturbs the normal formation, function, and clearance of the tear meniscus, leading to tear-film instability.[11,12,13,17]

Standard treatment for mild CCH utilizes non-invasive measures, including artificial oil, teardrops, and topical anti-inflammatory ophthalmic medications. Commonly available treatments for MGD at the time of this review include warm compress, Lipiflow™, iLux™, MiBoFlo ™, Sight Science's TearCare™, Intense Pulsed Light therapy, oral Omega oil supple-ments, oral and topical antibiotics, lid massages, and lid scrubs.[17] Overall, our study population consists of a diverse, complicated group of dry eye patients, as they

FIG.6 Improvement of total meibomian glands yielding liquid secretion post-treatment.

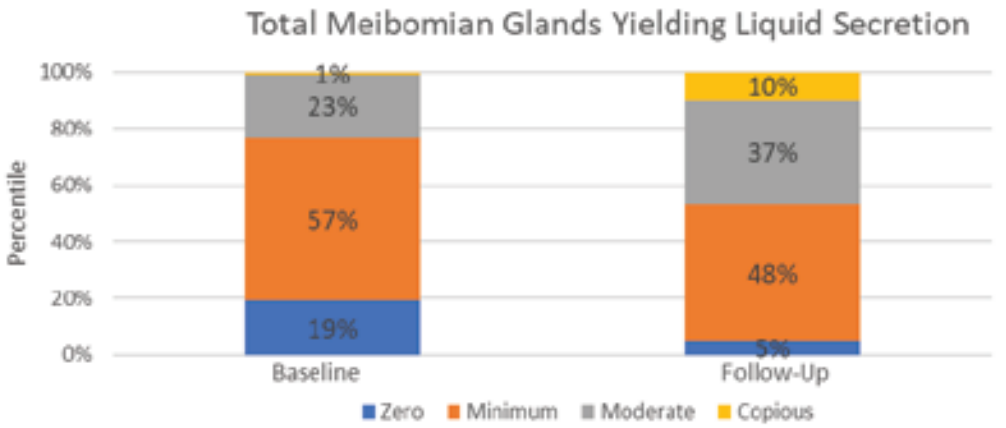

TABLE 3 Recorded Measurements during the Study

Measurement	Baseline	Follow-Up	Improvement	p-value
SPEED	15.6±7.0	10.3±7.1	5.2±6.7	0.001
NTBUT	10.1±5.7	11.3±5.8	1.3±5.6	0.177
Schirmer	11.3±7.9	12.7±6.3	1.4±6.9	0.178
MGYLS*	23.6%	46.8%	23.2%	<0.001
Tear Meniscus Height	0.4±0.2	0.3±0.1	0.2±0.2	<0.001

**MGYLS reported as percentage of subjects with moderate or copious secretion*

have a variety of ocular and non-ocular concomitant conditions. Also, many patients had extensive dry eye treatments pre-plication.

Notably, subject #7 had concurrent Filamentary Keratitis (FK), a corneal condition in which the epithelial layer adheres to the corneal surface, resulting in irritation and dry eye symptoms in addition to having floppy lids. This patient also had significant narrow-angle-glaucoma, which required a laser iridotomy procedure for both eyes. She experienced an unrelated onset of myocardial infarction in between treatments but completed the plication treatment procedures for both eyes.

Subject #9 had wet Age-related Macular Degeneration and required periodic anti-VEGF intraocular injection. This patient also had a medial ectropion (OD>OS) and ocular rosacea. Her DED symptoms fully improved after the plication treatment, which was coupled with "ignipuncture" (utilizing the RF to burn the inner aspect of the lower lid around the lower lid retractors) to fix the ectropion, assuming a better lid apposition for OD, and required only the proposed CCH plication and ThermaLid treatment for OS.

Other patients with comorbidities including ptosis, ocular rosacea, cataract, sleep apnea, a macular hole, pterygiae, superior limbic keratoconjunctivitis, nocturnal lagophthalmous, nasolacrimal duct obstruction, and atopy/allergy, were able to complete the study with positive outcomes without experiencing any major setbacks or significant related side effects.

As mentioned, our patients had chronic CCH and related DED that was refractive to the non-invasive traditional treatments. Therefore, we had to turn to surgical treatment, specifically cauterization-induced conjunctival plication, to seek a definitive solution for their condition. Treatment by cauterization improves

CCH by causing physical damage of the redundant folds, leading to shrinkage and flattened conjunctiva, which will provide better adhesion to the underlying sclera, thus allowing better tear-film distribution.[17] Dropping of the Tear Meniscus reflects the improvement in the inferior fornix "reservoir." This is because the gasket effect that holds the tear above the lid margin is reduced, allowing the tear to drop into the fornix. Reduced pleats and folds in the membrane also allow freer delivery of tears up from that reservoir to replace the used, exposed tear on the ocular surface. Coupled with ThermaLid treatment utilizing the 4MHz Monopolar Radiofrequency (RF) System, the combination therapy provides substantial objective and subjective improvements.

During post-procedure follow-up visits, patients reported significantly decreased SPEED scores, which indicate a substantial reduction in dry eye-related symptoms. Significant improvements in MYGLS and Tear Meniscus Height were also observed. NTBUT and Schirmer's score showed minor improvements. Improvements in MGYLS and NTBUT objectively indicated that the MGs responded well to the combination treatment. Improvement of Schirmer's test results may indicate better tear retention from reduced evaporation. This could also suggest a reduction in ocular inflammation from reduced evaporation, friction, and subsequent increased production of tear volume. The significant improvement in Tear Meniscus Height corresponds with restored inferior fornix reservoir function. Filamentary Keratitis resolved after the plication treatment in the affected patient and significant improvement of their dry eye symptoms. The patient, who suffered from medial ectropion, reported subjective symptoms resolved, coupled with clinical improvement evidenced by normalized tear osmolarity, decreased red scale, and much-improved Meibomian glands function bilaterally. The improvements experienced by this patient illustrated another possible use of the RF as ignipuncture helped to reconstruct the lower lid to improve ectropion.

Overall, the improvement of liquid oil production observed in Meibomian Gland Expression is the most significant finding from our study, as it showed that upon successful relief of obstruction, the non-functional glands could potentially revert to the functional state. Even in patients who had minimal functional MGs before treatment, both subjective and objective improvements improved the number of functional MGs clinically detected on exam. As mentioned, a prolonged obstruction can impair function, eventually leading to the Meibomian glands' truncation and atrophy. The decrease in liquid oil production from these glands will lead to symptoms of DED.[16]

During pre-treatment evaluation of the MGs, the glands' physical expression allowed for evaluation of total gland secretion at that point in time. The significantly greater number of functional glands after the ThermaLid treatment showed that treatment could remove the obstruction, allowing the previously clogged glands to function normally. Prolonged obstruction of MGs will lead to inactivation and eventually cause them to wither away. This could infer this treatment's ability to resuscitate and potentially save these glands, allowing them to perform their functions, reducing signs and symptoms of DED.

Patients who undergo this treatment rarely report side effects other than redness and minor ocular discomfort, which usually resolve after a couple of weeks of being on tapered antibiotic and steroid ophthalmic drops. Significant improvements in DED symptoms are reported during the follow-up visits as the eye heals and typically provide the impetus for treating the fellow eye.

One shortcoming of this study is that the plication treatment for CCH was coupled with the ThermaLid procedure that was performed on all participants. Therefore, it is not possible to parse out the degree of improvement relating to each treatment arm. However, from a pathophysiological standpoint, they go hand-in-hand, as the plication treatment smoothens the ocular surface to improve tear distribution, and the ThermaLid treatment enhances oil production that improves the tear itself. Fixing one without fixing the other would provide only a partial remedy in many of these cases.

The study's additional limitations include the retrospective study design and subjects having received treatments for symptoms before the RF treatment. Ideally, a prospective study with the RF device used to treat only the CCH or ThermaLid of one eye and CCH plus ThermaLid in the fellow eye, on patients who have not received treatments for DED before participation in the study, could be conducted to

determine the full clinical benefit of the treatment of DED symptoms with this technology.

CONCLUSION

The data collected from this study support the statement that a two-step approach utilizing a radiofrequency device to treat MGD-related DED patients, who also suffer from concurrent CCH, is a safe approach that can provide significant clinical improvements and relief from symptoms of DED. The use of the RF device yielded significant clinical improvements, especially when considering the study cohort's gamut of prior treatments. The added clinical benefit of combining multiple modalities is evident when treating MGD and CCH.

ACKNOWLEDGMENT

Especially helpful to this study was Alexander Denis, Clinical Data Associate from Cynosure, for his statistical analysis.

DISCLOSURE

Fina ncial:

- Dr. Jaccoma, MD, serves as a consultant for Cynosure
- Dr. Jaccoma, MD, is a co-inventor and part owner of the eyeThera thermaShield (eye shields used in this study)
- Liem Nguyen, BS, OMS-IV, has no potential conflict of interest

Device Use:

- The RF device used in this study is cleared by the FDA and indicated for the non-ablative treatment of mild to moderate facial wrinkles and rhytids as well as use in general surgical procedures in accordance with its instructions for use.
- The device is being used off label in this study to specifically treat dry eye symptoms, Meibomian Gland Dysfunction, and Conjunctivochalasis.

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