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Review Article

Current treatments for Meibomian Gland Dysfunction and Eye Lid Margin Disease

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Abstract

Importance: This study highlights the value of current therapeutic devices in the authors practice for the management of meibomian gland dysfunction (MGD) and eyelid margin disease (ELD).

Background: To evaluate the effects of current therapeutic devices on clinical measures of dry eye related to MGD and ELD in patients unresponsive to previous therapies.

Design: A retrospective chart review of patients treated at one site.

Participants: One thousand three hundred eighty-six eyes of 711 treated patients who were documented treatment failures with previous pharmaceuticals and/or devices were included in the patient population.

Methods: Treatments for MGD included: lid exfoliation, low level light therapy in combination or alone with intense pulsed light therapy (LLLT or LLLT/IPL), thermal pulsation, blink assisted thermal energy, and radiofrequency thermal energy all performed at one center.

Main Outcome Measures: Results included changes in the graded MGD score (grading scale 0 - 4), tear breakup time (TBUT), Ocular Surface Disease Index (OSDI) questionnaire score and lissamine green staining (LGS).

Results: Significant improvements in the MGD scores, TBUT, OSDI questionnaire scores and LGS were seen. There were no ocular or facial adverse events or side effects related to any of the treatments.

Conclusion: The application of an algorithm for the treatment of MGD and ELD is beneficial in the majority of patients who had failed to improve with alternative pharmaceutical and device interventions.

Keywords: Low Level Light Therapy (LLLT); Intense Pulsed Light (IPL); Meibomian Gland Dysfunction; Ocular Surface Disease Index (OSDI); Dry Eye Disease (DED); Eye Lid Margin Disease(ELD)

Introduction

Dry eye disease (DED), meibomian gland disease (MGD) and eyelid margin disease (ELD) are an ever-increasing problem in the general population which effects over 100 million patients [1-4]. Pharmacological treatment in diverse dry eye disease populations have been extensively covered and will not be the focus of this article [5,6]. The predilection for women is well known [7]. Gupta., *et al*. has shown the population continues to present at an earlier age [8]. Meibomian gland disease prior to ophthalmic surgery is a concern when dealing with refractive or refractive cataract surgery. Infectious keratitis and endophthalmitis after refractive and refractive cataract surgery are potentially devastating complications [9-11]. Currently in a single series with a single surgeon performing cataract surgery (KGS/N-39603) there have been zero reported

cases of endophthalmitis of which an aggressive treatment of eyelid margin disease is included. Also, in a single series with a single surgeon performing refractive surgery (KGS/N-78075) there have been zero reported cases of infection of which an aggressive treatment of eyelid margin disease is included. Stonecipher., *et al*. reported the second most common reason influencing the risk of an enhancement after laser vision correction is dry eye disease [12]. Aggressive treatment of MGD and DED can reduce this potential issue in this patient population. Finally, the concept of "perfect vision" in our refractive or refractive cataract patient depends on preoperative measurements and diagnostics. If we do not get the appropriate measurements before surgery the outcomes after surgery become mercurial. The treatment of MGD and ELD are imperative to the benefit of our patients receiving the safest and most efficacious outcomes so that we can improve symptoms, increase the rapidity of post-operative recovery, and most importantly improve vision in every patient without untoward results.

This paper is a review of the treatments in one clinic with one surgeon reviewing 1386 eyes of 711 patients treated for MGD and/or ELD prior to refractive or refractive cataract surgeries and in symptomatic patients.

Patients, Methods and Review of Results

Figure 1 shows the treatment algorithm that was used. The differentiation between anterior, posterior, or mixed disease drives clinical decision making. Each treatment modality and the results of their use is discussed in more detail below.

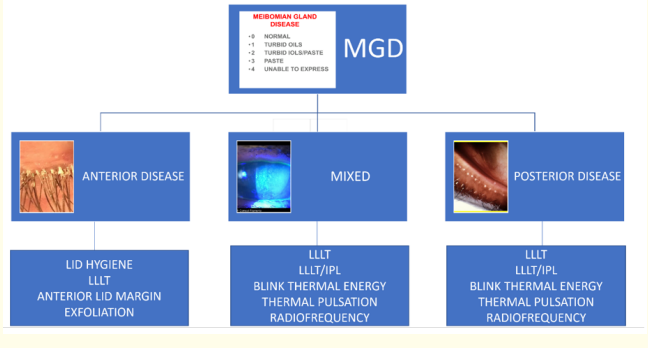

Figure 1: A breakdown showing the options included for grading and treatment of the patients included in the study based on disease type.

Anterior lid margin exfoliation (ALME) or microblepharoexfoliation (MBE)
(N-148)

ALME or MBE is either done in the office, at home or in conjunction with LLLT in the author's clinic. The design is to effectively remove bacterial biofilm and two species of mites (*Demodex folliculorum* and *Demodex brevis*). ALME in our clinic comes in two forms: Nulids (NuSight Medical, Escondido, CA, USA) and BlephEx® (Scope Ophthalmics, London, United Kingdom). In a multicenter trial, Nulids treatment showed > 51% improved OSDI scores, 65% improvement in TBUT, and over 80% improvement in meibomian glands yielding secretions [13]. Epstein., *et al*. have shown MBE to be an efficacious way to reduce lid margin infestation with Demodex [14]. In this review, ALME or MBE is used prior to refractive or refractive cataract surgery to improve diagnostics and to reduce the risk of infection. Improvement was noted with a single treatment in 81% of eyes, while 19% required additional treatments to improve symptoms or produce acceptable diagnostics prior to surgery.

Low level light therapy (LLLT) and intense pulsed light therapy (IPL)
(N-916)

Regarding LLLT and IPL, the authors use the Eye-light device (Espansione, Bologna, Italy) and EPI-C Mask® device (Espansione, Bologna, Italy). They utilize the unique and patented technologies of Light Modulation® and Optimal Power Energy®. Below are details of how they are used as solo therapy and in combination.

Low Level Light Therapy (LLLT) solo therapy
(N-232)

The primary effect of LLLT is localized transient "heating" of the absorbing chromophore based on electric or light oscillations. Beneficial effects of LLLT on the eye have been found in optic nerve trauma, methanol intoxication, optic neuropathy, retinal injury, retinitis pigmentosa, phototoxicity, and age-related macular degeneration [17,18].

Other key points include reducing epithelial turnover and reducing the risk of gland obstruction, activating fibroblasts, and improving collagen synthesis, minimizing demodex mite infestation, modulating the secretion of pro- and anti-inflammatory molecules, and reducing the concentration of MMPs by downregulating at the mRNA level and influencing reactive oxidative species (ROS) [19,20].

LLLT is used as red or blue light therapy. Red LLLT is absorbed by the mitochondria and stimulates ATP increasing cellular action which stimulates production of collagen, elastin, and thermal energy endogenously. The blue LLLT creates a bacteriostatic effect which is beneficial in patients with anterior lid margin disease, seborrhea, acne rosacea and acne vulgaris.

Pult., *et al*. compared IPL to LLLT and showed that LLLT treatment produced warming of the eyelids and with IPL only warming of the cheeks and temple were seen. LLLT treatment improved dry eye symptoms and the tear film. Notably the LLLT thermal effect was more significant for the upper eye lid than the lower eye lid (< 0.001) [21] (Figure 2).

Figure 2: Thermal photography after application of LLLT. The heat of the upper and lower eyelids, cheek, and temple before and after a single application of LLLT was measured with a thermal camera before (Tbefore) and directly after application in meibomian gland disease patients. After each application, the temperature was measured immediately (T0min), after 2 minutes(T2min), after 15 minutes (T15min) and 25 minutes (T25min).

Stonecipher., *et al*. showed in a 15-minute session of LLLT used 3 times in one week in dry eye patients who had failed previous pharmacologic, therapeutic, or combination treatments the significant improvements in TBUT ($p < 0.001$), lissamine green staining ($p < 0.02$), and MGD grading ($p < 0.001$) in 3 - 5 weeks. In addition to objective findings, subjective improvements in OSDI scores ($p = 0.002$) were also seen [22].

Currently, the authors use LLLT prior to surgery in a "perfect vision" system. The surgeon analyzes the preoperative diagnostics including topography, tomography, ray-tracing, and biometry as indicated prior to refractive or refractive cataract surgery. If standard deviations are not within normal limits, then the patients are treated with LLLT with or without manual expression and the tests are repeated one to two weeks later prior to surgery.

Low level light therapy in combination with intense pulsed light (LLLT/IPL) (N-684)

The authors do not advocate IPL alone. However, multiple studies have shown the benefits of IPL in dry eye disease [23-29]. In the treatment of patients with acne rosacea a more formal treatment protocol with IPL as the mainstay may be indicated but for us the combination has worked best. Stonecipher., *et al*. showed in a multicenter study of 460 eyes of 230 patients that mean OSDI scores were significantly lower after treatment. Over 70% of patients had pretreatment OSDI scores indicative of dry eye; this dropped to 29.1% after treatment. A 1-step or greater reduction in MGD grading was observed in 70% of eyes with 28% of eyes having a 2-step or greater reduction. Tear breakup time was ≤6 seconds in 86.7% of eyes pretreatment and dropped to 33.9% of eyes after treatment. There were no ocular or facial adverse events or side effects related to the combined light treatment. In this study the use of combined LLLT/IPL for the treatment of severe MGD is beneficial in patients who have failed topical and/or systemic therapy [30].

Low level light therapy (LLLT) for recalcitrant chalazia (N-40)

Although a nemesis to the eye surgeon's practice for years, recalcitrant chalazia are becoming a common finding with the increased use of masks with Covid 19 (personal observation). The use of LLLT for the treatment of recalcitrant chalazia has been reported by Stonecipher., *et al*. and Verbelli., *et al* [15,16]. Stonecipher., *et al*. reported 46% showing resolution with one treatment and 92% showing resolution with two treatments. Only 8% required traditional incision and curettage in this series [16]. The recent suggestion by the authors is a more rapid process than that suggested in the article. At present the patient is treated and if resolution is not seen within 24 - 72 hours retreatment is suggested. With this regimen complete resolution has occurred with one treatment in 50%, two treatments in 86% and in 100% with three treatments over a 72-hour period. No patients have required incision and curettage in this series over the last year (N-14).

Blink assisted thermal energy (N-114)

The authors currently use the Tear Care® System (Sight Sciences, Menlo Park, CA, USA) which delivers thermal energy to the upper and lower eyelids while the patient blinks naturally. While not studied extensively we have seen an 85% subjective improvement in patients utilizing this technology.

Thermal pulsation (N-48)

The two devices we use for thermal pulsation are the TearScience® LipiFlow® System (Johnson&Johnson, New Brunswick, NJ, USA) and the Systane® Ilux® system (Alcon, Geneva, Switzerland). The TearScience LipiFlow System has FDA approval for the application of localized heat and pressure therapy in adult patients with chronic cystic conditions of the eyelids, including Meibomian Gland Dysfunction (MGD), also known as Evaporative Dry Eye or Lipid Deficiency Dry Eye. Multiple studies have detailed the benefits of this technology and we are not going to cover those in this review [31-34]. Tuber., *et al*. have done an excellent review of both technologies and found both systems to be equally beneficial in statistically improving meibomian gland function yet with no statistically significant difference between the two technologies [35].

Radiofrequency thermal energy (RFTE) (N-120)

Radiofrequency as an applied treatment in MGD and ELD is a relatively new concept. Like IPL, RFTE started in dermatologic and cosmetic practices with anecdotal improvement in dry eye disease. When radio frequency is applied to collagen, heating allows tissue shape to change. This effect is produced with lower temperatures ranging between 43 - 45 degrees Celsius to avoid skin necrosis. Tissue hyperthermia with heating of tissue is the result.

The wound healing response heat is applied to the epidermis leading to the following phases:

1. **Inflammatory phase (1-3 days):**
    a. 5 - 10 minutes: Early contraction of blood vessels
    b. Hours to 1 - 3 days: Vasodilation to increase blood supply
    c. Cells (macrophages, neutrophils) infiltrate the damaged area to remove dead/damaged tissue and destroy bacteria.
2. **Proliferative phase (ongoing process over 3 weeks as tissue is repaired):**
    a. Day 2-3: Fibroblast activity is induced in damaged tissue. Fibroblasts multiply, sending mediators to stimulate repair, combining with damaged tissue
    b. Day 5-7: Fibroblasts begin synthesis of collagen
    c. Day 7-21: Old collagen is removed by collagenase.
3. **Maturation Phase (3 weeks to 6 months and beyond)**
    a. New collagen is generated
    b. Elastin becomes more uniform, and its quality is improved.

RFTE utilizes energy created by a high frequency alternating current. The resistance of the tissue to the passage of this current creates heat internally in the tissue. The energy creates molecular heat within each cell, volatilizing (i.e. vaporizing) its water and splitting the tissue at the cellular level. This vapor serves to act as a coagulating factor. The frequency of the Tempsure® Envi (Cynosure, Westford, MA, USA) RFTE device (which the author uses) is 4.0 MHz, creating 4 million cycles per second. This allows consistent energy control and quick healing of tissue [36].

RFTE heats tissue by passing a high frequency current through the tissue. The tissue is the heating element by its impedance, the electrode is merely how the current is introduced. Currently the study population is limited but 86% of patients who have failed many of the above discussed treatment options report success with one treatment that has lasted up to one year.

Discussion

MGD and ELD are common presentations today in a comprehensive practice, refractive surgery, and refractive cataract surgery [37-39]. With increased screen time on computers and devices the authors have seen increasing dry eye disease. Previous pharmacologic interventions have resulted in significant improvement but with the addition of the aforementioned devices, patients have new treatment options [40,41]. With COVID-19 and increased mask wear the increase in dry eye and chalazia presenting to the physician is more common and now the physician has more options to choose to individualize treatments.

Conclusion

Treating MGD and ELD is an essential addition to the practice. Following a simple algorithm adds value and with lack of third-party reimbursement for these treatments, patients like to have an idea what their options and chance of success are prior to investment. Preoperative treatment of the refractive and refractive cataract patient helps with postoperative success and patient satisfaction.

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