• Clinical Research •

The ILux® compared to the mechanical meibomian gland expression for the treatment of moderate and severe meibomian gland dysfunction

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Abstract

● **AIM:** To compare the safety and effectiveness of eyelid treatment with the ILux®-MGD Treatment System in one session versus five sessions of mechanical meibomian gland expression (MMGE) in patients with moderate to severe meibomian gland dysfunction (MGD).

● **METHODS:** A prospective, randomized, open-label, and controlled clinical trial that compared one session of the ILux® MGD Treatment System versus five sessions of MMGE in both eyes of 130 patients aged ≥18y with Ocular Surface Disease Index (OSDI) scores ≥13, total meibomian gland scores (MGS) of <15 in the lower eyelid of each eye, and non-invasive tear break-up time (NI-TBUT) <10s, who were randomized 1:1 to ILux® or MMGE.

● **RESULTS:** The mean age was 58±17.49y. Baseline total MGS scores in both treatment groups were comparable. During follow-up, there were significant differences in total MGS and per sector with *P*<0.001. Multivariate analysis was performed using generalized estimating equations corresponding to the generalized linear model for repeated means to determine the treatment relationship with total MGS, NIBUT, and OSDI. There was a significant difference between ILux® and MMGE (*P*<0.001) at follow-up from the first to the twelfth month in MGS, NI-BUT, and OSDI scores. No adverse events were reported.

● **CONCLUSION:** ILux® treatment compared to MMGE significantly improves symptoms and signs in patients with moderate to severe MGD for one year without adverse events.

● **KEYWORDS:** meibomian gland dysfunction; ILux®; ocular surface; dry eye

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INTRODUCTION

Meibomian glands (MG) are responsible for the secretion of lipids (meibum) into the ocular surface and have a protective role for tear film against evaporation[1-3]; therefore, meibomian gland dysfunction (MGD) is associated with evaporative dry eye (EDE)[3-5]. Dysfunctions characterized by reduced MG expressibility, low meibum quality, and eyelid margin inflammation lead to hyperkeratinization and hyperviscosity. Finally, atrophy and dropout of MGs in some cases could appear[6-7].

MGD is a prevalent dry eye disorder (DED) with an estimated prevalence range between 3.5% and 70%[1,8-10], it constitutes the primary underlying pathology within the EDE subtype[11-12]. In addition, it is known that MGD is a chronic and progressive condition[2,13], so it is crucial to identify clinical approaches that can successfully address this underlying condition.

MGD management typically includes using artificial lubricants, topical lipid supplements, lid hygiene, warm compression or heat application, omega-3 supplementation, topical and systemic antibiotics for treating *Demodex* mites infestation, and steroids[14-16].

Mechanical therapy includes debridement-scaling of the line of Marx and the lower lid margin[17], as well as other techniques for manually expressing the glands. This approach is based on the understanding that effective treatment of MGD entails the removal of glandular contents by various techniques[18-19].

Eyelid thermal pulsation devices enable the application of heat at the suitable temperature to the surface of the eyelids, while also expressing the glands to remove their contents[20] and have been shown to improve signs and symptoms over 12mo in cases with severe meibomian obstruction[21].

The ILux® MGD Treatment System, developed by Alcon in Fort Worth, Texas, is a device used to treat MGD. It consists of a disposable patient interface device and a handheld battery-powered instrument. The system applies both heat and compression to the eyelids, resulting in localized treatment for MGD. Clinical studies have demonstrated significant improvements in MG function within one to four weeks of using this system[20,22].

Prior to the implementation of vectored thermal pulsation therapies, the disadvantages of in-office mechanical meibomian gland expression (MMGE) included the discomfort caused by forcefully emptying the glands[23], the challenge of maintaining the eyelid temperature at a therapeutic level of at least 40°C[24], and the limited duration of the treatment's effectiveness, which was observed to last only one month[25]. For our patients, we have performed five sessions a year of this combination treatment for moderate and severe MGD.

This study aims to compare the safety and effectiveness of eyelid treatment in one session with the ILux® MGD Treatment Device versus five sessions in-office of MMGE in patients with moderate to severe MGD at one-year follow-up.

SUBJECTS AND METHODS

Ethical Approval The study was performed under the approval 2020001-00 of the Research Center of Clínica de Oftalmología de Cali, and all tenets of the Declaration of Helsinki for the protection of human subjects in medical research were strictly observed, and all subjects provided written informed consent before any study-related procedures. We have successfully registered our trial with ClinicalTrials.gov, and registration number: NCT06278584.

Study Design This prospective, randomized, open-label, controlled clinical trial compared one session of the ILux® MGD Treatment System with five sessions (baseline, 1, 3, 6, 9mo) of MMGE for the treatment of MGD.

Randomization After verification of the eligibility criteria, subjects in each group will be randomized 1:1 to the manual meibotherapy or ILux® group. ILux® labels and manual meibotherapy labels are made, the labels are then inserted into sealed envelopes, and then without knowing the content, the envelopes are sequentially numbered. Before treatment, the personnel assigned to perform the treatment will open the lowest-numbered envelope. The envelope number will be documented on the study source documents and in the database.

Inclusion Criteria The criteria for inclusion were as follows: participants are at least 18 years old, have a self-reported history of dry eye symptoms for two months before the study, and have a diagnosis of MGD. The delivery type is low, with both obstructive and non-cicatricial mechanisms. The scores for these mechanisms are as follows: The Ocular Surface Disease Index (OSDI) questionnaire ≥13, non-invasive tear break-up time (NIBUT) <10s (Sirius anterior segment analyzer, CSO, Florence, Italy), meibomian gland scores (MGS) <15. Ocular lubricant treatment (Systane® BALANCE, USA) will be used in all patients in both groups. Regarding atrophied glands, up to 6 in the lower lid were permitted.

Exclusion Criteria The exclusion criteria were: medical history includes a record of ocular surgery, allergic conjunctivitis, seborrheic dermatitis, rosacea, psoriasis, punctal plugs or previous punctal cautery, anterior or demodex blepharitis, cicatricial lid margin disease, ocular injury or trauma, chemical burns, limbal stem cell deficiency, active ocular infection or non-dry eye inflammation, aqueous-deficient dry eye, irregular cornea, lid abnormalities, and systemic disease conditions and medications that can lead to dry eye.

Study Parameters

Primary endpoints Effectiveness was defined as changes from baseline to 1, 3, 6, 9, 12mo in NIBUT and MGS. Using a Meibomian Gland Evaluator (MGE 1000) device to grade a total score for 15 MG in the lower eyelid evaluated in 3 regions: nasal (5 glands), medial (5 glands), and temporal (5 glands) expressed & graded from 0 to 3 (0=no secretion, 1=inspissated, 2=cloudy, 3=clear liquid).

Safety was defined as the incidence of device-related adverse events, including lid margin burns and alterations such as floppy eyelids, entropion or ectropion, and loss or burning of eyelashes.

Secondary endpoints In the OSDI, effectiveness was defined as changes from baseline to 1, 3, 6, 9, and 12mo. Safety was defined as discomfort and pain during treatment. A subjective pain scale will be used. Subjective reports of discomfort shall be recorded on a scale of 0-10. Specific scores on the scale included: 0=no discomfort or pain, 2=slight or transient awareness of pressure without pain, 4=moderate discomfort with minimal pain, 6=moderate pain, 8=severe pain, 10=intolerable pain. About safety, changes in corrected distance visual acuity (CDVA), cornea and conjunctival surface staining post-treatment (fluorescein and green lissamine), and intraocular pressure (IOP).

Exploratory endpoints We analyze the number of atrophied glands at baseline and each follow-up visit and changes in CDVA and cornea and conjunctival surface staining post-treatment (fluorescein and lissamine green).

Treatment

Mechanical meibomian gland expression Both eyes were treated on the same day (baseline, 1, 3, 6, 9mo), and applying

standard anesthetic eye followed the removal of eye makeup drops to both eyes. Local heat from an electrical warming mask for 10min was used. Later, a standardized device (Arita MG Compressor, Katena) applied a standard force to individual glands located at the under lid's temporal, center, and medial zone to drain them of their meibomian lipid. For 15s to obtain drainage effect and then repeat expression once after partial recovery cleared the ducts of contained secretion in about half the time taken to drain them initially. Adverse events were monitored throughout treatment and for 1h afterward.

ILux® Both eyes were treated on the same day (day 0, baseline), eye makeup was removed, and anesthetic eye drops were instilled into both eyes. The lower lid at the temporal, central, and nasal region was treated following instructions described in the user's manual for that device. Adverse events were monitored throughout treatment and for 1h afterward.

The ILux® MGD Treatment System is an eyelid thermal pulsation system with a single-use patient interface device and a handheld battery-powered instrument. All materials that contact the patient are made from biocompatible medical-grade silicone. The instrument component features a superior magnifying lens that allows the doctor to observe the eyelid margin during treatment. The instrument utilizes LEDs to generate light energy, which is passed through the outer pad to warm the eyelid tissue. The LEDs are positioned behind a transparent aperture on the exposed side of the shroud. Lime-green (568 nm) and near-infrared (850 nm) are two wavelengths of light. Chromophores in the eyelid absorb the light energy and heat the surrounding tissue. The system is designed to protect against unintended exposure to light. During a treatment temperature sensor, the inner pad and eye shield block light transmission directly into the eye and measure the inner and outer eyelid temperatures to maintain a meibum melt temperature of 38℃–42℃. These sensors automatically turn off the LEDs when the inner and outer eyelid temperatures exceed 44℃ and 45℃, respectively.

Sample Size Estimation The variation of the mean MGS of five points between ILux® and manual treatment, with a standard deviation (SD) of 8, was considered a clinical sample, obtaining a sample size for each group. It was 26, with a confidence level of 95% and a test power of 80%. For NIBUT, relevant differences between ILux® and manual treatment of 1.60s and SD of 3s were considered; the sample size obtained for each group was 57, with a confidence level of 95% and test power of 80%. At last, the OSDI score between ILux® and manual treatment of 10 points with SD of 17 was considered a relevant difference for the sample size for each group of 47 with a confidence level of 95% and test power of 80%. A sample size of 60 patients was obtained for each group (ILux® and manual treatment).

Table 1 Comparison of MGS by treatment according to follow-up time

mean±SD

Follow-up time	Treatments		*P*
	iLux	Manual expression	
Baseline	5.79±1.92	6.19±1.76	0.084
Month 1	10.34±2.15	6.98±1.79	<0.001[a]
Month 3	10.53±2.21	7.55±1.78	<0.001[a]
Month 6	10.46±2.6	7.47±1.62	<0.001[a]
Month 9	10.44±2.27	7.28±1.57	<0.001[a]
Month 12	9.97±2.07	7.32±1.63	<0.001[a]

MGS: Meibomian gland scores; SD: Standard deviation; [a]*P*<0.05, based on the Mann-Whitney test.

Statistical Analysis The analyses were carried out with the RStudio package, where descriptive statistics were used to represent the quantitative variables through central tendency and dispersion measures. The assumptions of normality were evaluated in the quantitative variables using the Shapiro test; the application of the RStudio package based on the ggplot2 program, specifically the ggstatsplot and ggwithinstats functions, will be used to compare the follow-up of patients within the ILux® and manual expression groups, using the Friedman test. On the other hand, the different variables between the ILux® and manual expression groups were compared at all evaluation times, for which the Mann-Whitney test was used. Multivariate analysis was performed using generalized estimating equations corresponding to the generalized linear model for repeated means to determine the treatment relationship with MGS, NIBUT, and OSDI measurements during follow-up. Statistical significance was considered for $P<0.05$.

RESULTS

One hundred thirty-one patients were analyzed to compare the efficacy of one session of the ILux® MGD Treatment System with five sessions (baseline, 1, 3, 6, 9mo) of MMGE for treating MGD. Totally 29.01% (n=38) were men, and 70.99% (n=93) were women; the average age was 58y (SD=17.49). Sixty-five patients were included in the ILux® and sixty-six in the MMGE group.

Comparing the MGS ILux® treatment group and manual expression, no significant differences were observed for the total MGS at baseline; thus, patients had the same conditions for the treatments provided. During follow-up, between month 1 and month 12, significant differences in total MGS and per sector with $P<0.001$ (Table 1).

A multivariate analysis was performed using generalized estimating equations corresponding to the generalized linear model for repeated means to determine the treatment relationship with total MGS. Treatment with ILux® was related to total MGS during follow-up with $P<0.001$. The positive β coefficient (1.96) indicates that total MGS is increased for patients with ILux® treatment compared to those who underwent MMGE.

When comparing the follow-up of the patients within each treatment, the following was observed for the total MGS (Figure 1). For treatment with ILux®, significant differences were observed with $P<0.001$, where the differences were between baseline 5.79 concerning month one of 10.34, 3mo of 10.53, 6mo of 10.46, 9mo of 10.44, and 12mo of 9.97. Significant differences were observed in the treatment with manual expression with $P<0.001$.

Comparing the mean NIBUT by the ILux® treatment group and manual expression group, the following was observed (Table 2). At baseline, there were no differences between treatments, indicating that the patients were in the same condition concerning the NIBUT. During the follow-up from month 1 to month 12, significant differences in NIBUT were observed with $P<0.001$.

A multivariate analysis was performed using generalized estimating equations for repeated means, and the relationship between treatment and NIBUT was determined. The results showed that treatment with ILux® was related to NIBUT during follow-up with $P<0.001$, where the positive β coefficient (1.93) indicates that NIBUT is increased for patients with ILux® treatment compared to those with hand expression.

In comparison of the patient follow-up within each treatment, the following was observed for NIBUT (Figure 2). For treatment with ILux®, significant differences were observed with $P<0.001$, where the differences were between baseline 5.03s concerning month one 8.49s, 3mo of 8.80s, 6mo of 8.69s, 9mo of 8.82s, and 12mo of 8.49s.

In the treatment with manual expression, significant differences were observed with $P<0.001$, with the differences between the basal moment of 5.26s concerning the first month of 6.73s, 3mo of 7.39s, 6mo of 7.39s, 9mo of 7.28s, and 12mo of 7.26s.

When comparing the OSDI by type of treatment, the following was observed (Table 3). At baseline, significant differences were observed with $P=0.009$. During follow-up, between month one and month 12, significant differences were observed in the OSDI with $P<0.001$.

In the multivariate analysis, the treatment's relationship with the repeated OSDI measurements was determined. The results showed that treatment with ILux® was related to OSDI during follow-up with $P<0.001$, where the negative β coefficient (-0.33) indicates that OSDI is decreased for patients with ILux® treatment compared to those treated with manual expression.

When comparing the follow-up of the patients within each treatment, the following was observed for the OSDI (Figure 3). For treatment with ILux®, significant differences were observed with $P<0.001$, where the differences were between baseline 41.45 concerning the first month 18.37, 3mo of 15.50, 6mo fo 17.07, 9mo of 15.85, and 12mo of 16.62.

In the treatment with manual expression, significant differences were observed with $P<0.001$, with the differences between the basal moment of 46.61 concerning the 1mo of 32.32, 3mo of 22.14, 6mo of 22.97, 9mo of 24.12, and 12mo of 26.20.

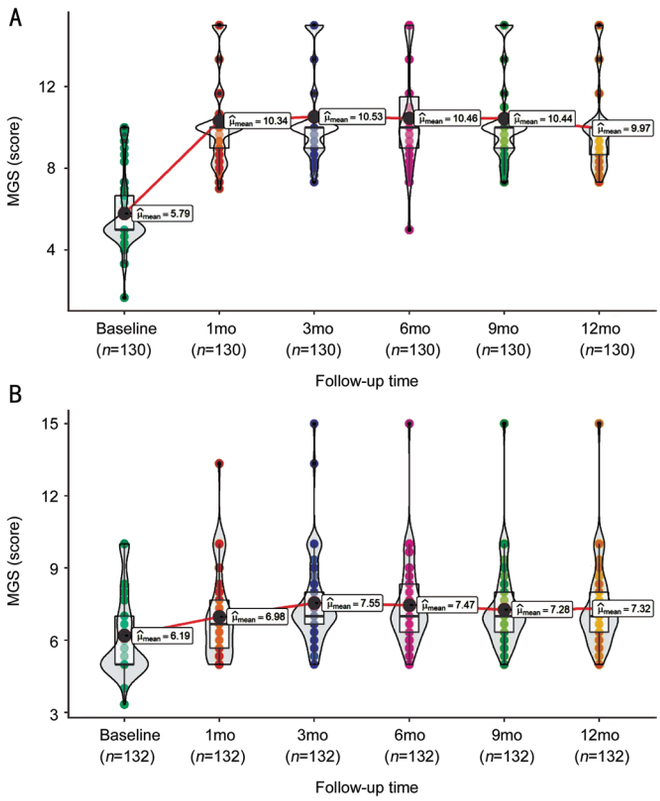

Figure 1 Meibomian gland score (MGS) comparison by follow-up time according to treatment A: ILux; B: Mechanical expression.

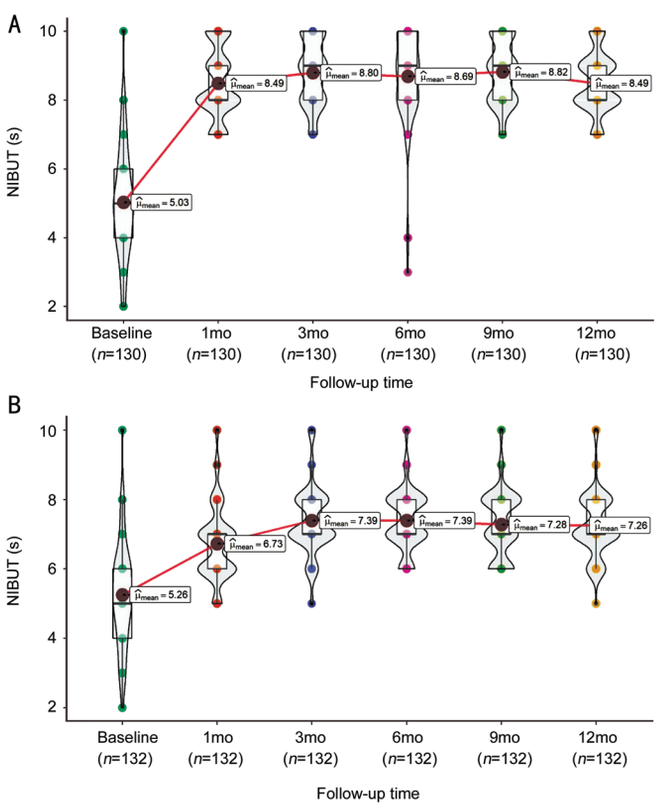

Figure 2 Comparison of Non-Invasive Tear break-up time (NIBUT) by follow-up time according to treatment A: ILux; B: Mechanical expression.

Table 2 Comparison of NIBUT by treatment according to evaluation time mean±SD

Follow-up time	Treatments		*P*
	iLux	Manual expression	
Baseline	5.03±1.59	5.26±1.5	0.154
Month 1	8.49±1.02	6.73±1.07	<0.001[a]
Month 3	8.8±0.96	7.39±1.02	<0.001[a]
Month 6	8.69±1.28	7.39±0.88	<0.001[a]
Month 9	8.82±0.91	7.28±0.95	<0.001[a]
Month 12	8.49±0.87	7.26±0.93	<0.001[a]

NIBUT: Non-invasive tear break-up time; SD: Standard deviation, [a]*P*<0.05, based on the Mann-Whitney test.

Table 3 Comparison of OSDI by treatment according to evaluation time mean±SD

Follow-up time	Treatments		*P*
	iLux	Manual expression	
Baseline	41.45±19.6	46.61±16.2	0.009[a]
Month 1	18.37±11.34	32.32±15.11	<0.001[a]
Month 3	15.5±9.34	22.14±7.47	<0.001[a]
Month 6	17.07±12.66	22.97±8.18	<0.001[a]
Month 9	15.85±8.77	24.12±6.37	<0.001[a]
Month 12	16.62±9.26	26.2±5.93	<0.001[a]

OSDI: Ocular Surface Disease Index; SD: Standard deviation; [a]*P*<0.05, based on the Mann-Whitney test.

When comparing the pain scale between the treatments, significant differences were observed with *P*<0.001, where the means of the scale were two for ILux® *vs* four for manual expression (Figure 4).

DISCUSSION

Many studies have evaluated several medical treatment strategies and devices for managing MGD; However, although there is no existing gold standard treatment for MGD[7], advances have been made to improve MG function and evacuation of retained gland contents. As per the definition of MGD by the International Workshop on Meibomian Gland Dysfunction (IWMGD)[7,26], the presence of terminal duct obstruction stands as a pivotal characteristic within the disease process. Therefore, the mechanical opening of the terminal duct and meibum expression play an essential role in the management[7,27].

Expression glands methods have been used for mechanical compression[23] and intraductal MG probing[28] and electronic heating devices such as LipiFlow®[29-30] (Johnson & Johnson Vision, USA), MiBo Thermoflo® (Mibo Medical Group, USA)[31], and ILux®[20]. Blackie *et al*[21] have shown sustained improvement in MG function and dry eye symptoms with a single 12-minute of vectored thermal pulsation procedure (VTP), Lipiflow® procedure over 12-36mo; the present study is a long-term follow-up of a cohort of subjects that documented

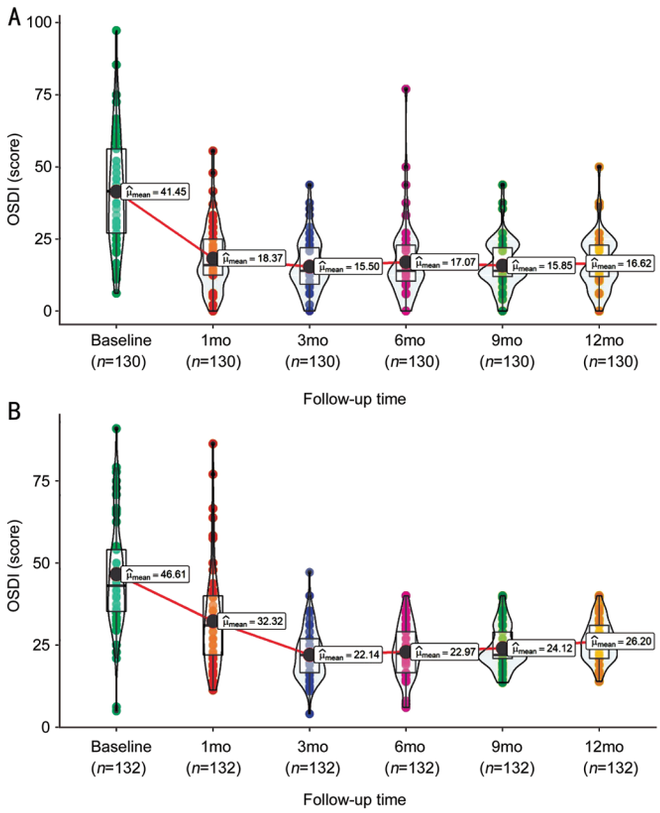

Figure 3 Ocular Surface Disease Index (OSDI) comparison by follow-up time according to treatment A: ILux; B: Mechanical expression.

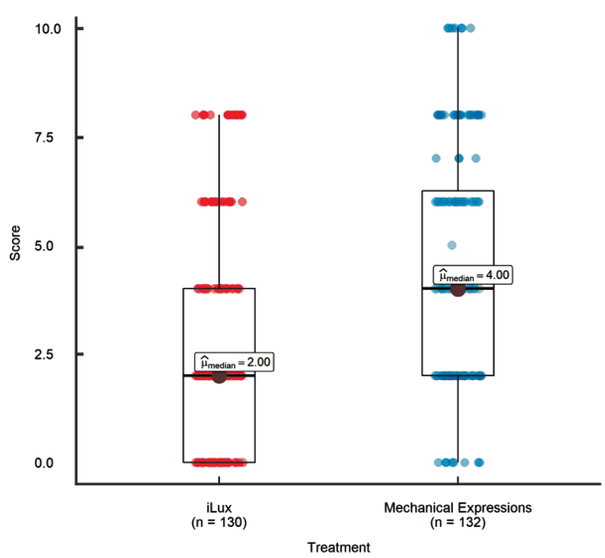

Figure 4 Pain scale comparison by treatment.

the significant improvement in dry eye signs and symptoms sustained at twelve months after a single treatment with the ILux® MGD Thermal Pulsation System.

One recent study found improvement in MGD-related symptoms and a decrease in inflammation of the eyelids after using 0.05% nano-cyclosporine in patients with MGD. They did not use any expression method, and they suggested that the nano-emulsion cyclosporine formulation has the potential to control inflammation caused by dry eye with MGD[32]. This study result is significant because, as mentioned by Rao *et al*[33], inflammation in DED also results in changes in the MGs, and

MGD further perpetuates the cycle of DED, resulting in a vicious circle.

The ILux® MGD Thermal Pulsation System is a handheld in-office device that allows the application of localized heat and pressure while simultaneously visualizing the MGs. Previous studies have demonstrated the ability of ILux® to alleviate signs and symptoms of dry eye in patients with MGD until one year[20,22,34].

Our study showed that one treatment session with ILux® and five sessions of manual expression significantly reduced the signs and symptoms of MGD. Studies have followed the secretory recovery of single MGs after drainage by compression or manual expression[35-36], furthermore is necessary for several therapy sessions. Lee *et al*[25] report a regimen of four mechanical sessions within a month, alongside at-home treatment, albeit the study's follow-up period spanned only one month.

Various treatments result in more pain, discomfort, and difficulty with patient treatment adherence. Korb and Blackie[23] found that a significant amount of force is required to evacuate the MG contents. The pressure applied to the lower lid results in substantial discomfort, which most patients cannot tolerate. In our study, pain and discomfort were well managed in the ILux® group and significantly less in the mechanical group.

For the mechanical expression group, we performed five sessions in one year, and we obtained a reasonable control of symptoms and signs; there is no standard for frequency; for example, another study used the routine of the patient's home therapy and reported therapeutic expression may be necessary several times a year (2-12 times)[23].

At baseline, the ILux® and mechanical expression groups were similar concerning the mean non-invasive tear break-up time and MGS, with a significant difference in the mean OSDI score. In both treatment groups, all three efficacy measures showed improvement from baseline beginning at the 1-month follow-up and were sustained for 12mo. There is no cost-benefit comparison between the two methods; however, patients might favor achieving superior results in a single, painless session rather than undergoing five separate sessions.

Although both treatments exhibited improvement, upon comparing the treatment regimens, ILux® demonstrated notably superior outcomes in terms of OSDI score, NIBUT, and MGS in comparison to mechanical expression across all follow-up assessments.

There are some limitations to this study. 1) Meibography was not conducted to evaluate the initial severity of meibomian gland atrophy and any subsequent changes; 2) Endpoints other than MGS were not controlled for, particularly when assessing OSDI; 3) The assumption was made that the patient's condition remained consistent over time, despite the occurrence of day-to-day exacerbations and seasonal variations, making this study a preliminary investigation for further research.

Our study is the first to compare one ILux® session to a regimen of five sessions of MMG in-office. Our results indicate significant advantages concerning signs and symptoms of dry eye and MGD over one year in subjects with moderate-to-severe baseline MGD. These findings provide additional evidence for the relative efficacy of ILux® and utility in treating MGD.

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