# Study protocol

Diamond bur Microblepharoexfoliation Combined with Intense Pulse Light and Meibomian Gland expression for Evaporative Dry Eye: A Short-term Controlled Study.

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## 1. Introduction

Dry eye disease (DED) is a chronic multifactorial disease of the ocular surface characterized by a loss of homeostasis of the tear film, which is accompanied by ocular symptoms caused by hyperosmolarity, ocular surface inflammation and neurosensory abnormalities [1,2]. DED prevalence varies according to the definition used and the characteristics of the population studied, but it ranges from 5% to 50%, is more frequent in women and increases with age [3]. Currently, evidence suggests that all forms of DED have an evaporative component because without evaporation, hyperosmolarity cannot occur [4].

Meibomian gland dysfunction (MGD) is the most common etiology of tear film evaporation, and it is characterized by the obstruction of meibomian glands due to terminal duct obstruction and/or changes in meibum quality and quantity [4,5]. The management and therapy subcommittee of the TFOS DEWS II recommended intense pulsed light (IPL) as a second step therapy for MGD when education, lid hygiene, warm compresses and ocular lubrications do not achieve the desired effect [6]. IPL is a form of light therapy that uses flash lamps to emit noncoherent, polychromatic high-intensity light of determined wavelength spectrum, ranging from 500 to 1200 nm [7]. Using these wavelengths, the potentially harmful ultraviolet radiation, which occurs below 500 nm, is filtered [8]. In 2002, Toyos et al. reported that patients with dry eye disease (DED) who received IPL treatment for rosacea, acne or other skin disorders reported improvements in their dry eye symptoms [9]. This finding led to the development of different IPL devices to specifically treat DED. Currently, different studies have shown that IPL is a safe and effective treatment that improves the signs and symptoms of patients with DED owing to MGD [9–15]. The main mechanism of action of IPL is thermal. IPL energy absorbed by hemoglobin which causes thrombosis of abnormal blood vessels reduces the concentration of inflammatory mediators in the eyelid and meibomian glands, thus preventing their dysfunction and improving meibum flow [16].

Combined or additional therapies in MGD treatment have emerged such as Microblepharoexfoliation (MBE). MBE is a novel in-office treatment that works by exfoliating the eyelid margins to remove the accumulated biofilm debris, epithelial keratinization and capped meibomian glands, resulting in better meibum outflow. Different studies have shown that MBE improves DED symptoms [17,18], demodex blepharitis [17–20] and meibomian gland function [18,19,21] In addition, meta-analyses recommend combining IPL with meibomian gland expression (MGX) compared to IPL or MGX alone [22–24].

However, to the best of our knowledge, we have not found any studies evaluating the benefits of MBE combined with IPL and MGX.

Consequently, the purpose of the current study is to evaluate whether MBE combined with IPL and MGX leads to an improvement of symptoms and signs in patients with DED due to MGD.

## 2. Methods

This prospective, unmasked, non-randomized and controlled study was approved by the clinical research ethics committee of the University of Murcia (ID: 4097/2022), adhered to the tenets of the Declaration of Helsinki, and was performed at the Novovision Ophthalmology Clinic from April 2022 to January 2023. Informed consent was obtained from each patient before enrollment in the study.

### 2.1 Subjects

Patients with DED due to MGD attending Novovision Ophthalmology Clinic were enrolled. The inclusion criteria were as follows: (1) age ≥ 18 years old; (2) DED diagnosis according to DEWS II [25] meeting one of the following conditions: (2.1) ocular surface disease index (OSDI) score ≥ 13; (2.2) NIBUT < 10 seconds; and (2.3) ocular surface staining with > 5 or 9 corneal or conjunctival stains, respectively, and (3) MGD diagnosis according to the international workshop on MGD [26] meeting two of the following conditions: (3.1) irregularity of the eyelid margin or mucocutaneous junction; (3.2) vascularity of the eyelid margin; (3.3) plugged or capped Meibomian gland orifices; (3.4) Meibomian gland atrophy; or (3.5) decreased meibum quality and quantity. The exclusion criteria included: (1) skin pathologies that prevent IPL treatment; (2) all corneal disorders that affect diagnostic tests, such as: (2.1) active corneal infections; and (2.2) corneal dystrophies; (3) active ocular allergy; (4) pregnant or lactating women; and (5) patients who did not understand or comprehend the informed consent. Systemic or ocular diseases, previous systemic or ocular treatments and ocular surgeries with more than 6 months of postoperative evolution were not considered exclusion criteria to better reflect the patient population. Contact lens users were instructed not to wear their contact lenses one week before baseline and follow-up examinations.

### 2.2 Experimental design

A flowchart showing the experimental design of the study is presented in Fig.1. Patients with MGD were classified into the treatment and control groups. All patients received a home-based therapy based on Therapearl eye mask warming compress (Bausch & Lomb, Madrid, Spain) twice a day and Eyestil synfo

eyedrops (Sifi Iberica SL, Madrid, Spain) 4 times a day during the study including the follow-up period. Treatment group patients also underwent a series of three combined treatment sessions of MBE, IPL and MGX at 2-week intervals. All patients underwent a 2-months follow-up from baseline.

### 2.3 Clinical assessment

Parameters were assessed with the S390L Firefly WDR slit lamp (Shangai Mediworks Precision Instruments Co. Shangai, China) that includes a dry eye module designed to perform objective and non-invasive measures, which are analyzed by an artificial intelligence (AI) identification system (Mediview R3.0 software). To asses treatment efficacy, parameters were measured at baseline and the last visit. DED symptoms were assessed with the ocular surface disease index (OSDI) and symptom assessment in dry eye (SANDE) questionnaires. Ocular surface measurement was carried out by one examiner (ABS) in the following sequence to best preserve the integrity of the tear film to avoid affecting the test results: (1) tear film stability and volume; (2) ocular hyperemia; (3) ocular surface staining (OSS) and (4) meibomian gland analysis. Except for OSDI and SANDE questionnaires, which were collected per subject, all other clinical outcomes were collected per eye. To evaluate treatment safety, post-treatment adverse events were reported.

#### 2.3.1 Tear film stability and volume

Tear film stability was evaluated automatically by the AI identification system via detection of the first (F-NIBUT) and average noninvasive tear film break-up time (A-NIBUT) using a Placido disc. To assess the lipid layer grade (LLG), the lipid layer interferometric pattern was compared with the lipid layer thickness (LLT) grading scale template provided by the device, which has the following values: 1; LLT < 30 nm; 2, LLT of 30-60 nm; 3, LLT of 60-80 nm and 4, LLT >80 nm. Regarding tear volume, tear meniscus height (TMH) and tear meniscus area (TMA) were also automatically assessed by the AI identification system through focused image of the lower eyelids.

#### 2.3.3 Ocular Hyperemia

Ocular hyperemia was assessed through complete picture of the ocular surface focused on the bulbar conjunctiva. Nasal ciliary hyperemia (NCIH), temporal ciliary hyperemia (TCIH), nasal conjunctival hyperemia (NCOH) and temporal conjunctival hyperemia (TCOH) were analyzed automatically the AI identification system with a value between 0% (no hyperemia) and 100% (the highest level of hyperemia).

### 2.3.4 Ocular surface staining

OSS was subjectively and invasively evaluated with the oxford grading schema reported by Bron et al. [27]. Prior to assess OSS, a single drop of unit dose saline was instilled onto a fluorescein-impregnated strip. The right lower lid was then pulled down and the strip was tapped onto the lower tarsal conjunctiva. The same procedure was carried out on the left. A cobalt-blue filter with yellow Kodak Wratten 12 barrier filter was used for a better detection of fluorescein staining.

### 2.3.5 Meibomian gland analysis

Meibomian gland analysis was performed on the upper and lower eyelid using infrared light after everting the eyelids with a cotton swab. the AI identification system automatically analyzed the meibomian glands, obtaining the upper loss area Meibomian gland (U-LAMG) and lower loss area Meibomian gland (L-LAMG) with a value between 0% (no glandular dropout) and 100% (the highest level of glandular dropout), and upper meibomian gland dysfunction grade (U-MGD grade) and lower meibomian gland dysfunction grade (L-MGD grade), which have the following values: 0, no MGD; 1, mild MGD; 2, moderate MGD and 3, severe MGD.

Meibomian gland secretion was assessed by MGX. Fifteen glands on the lower eyelids were evaluated. For each gland, the secretion had the following scores: 0, no secretion; 1, inspissated/toothpaste consistency; 2, cloudy liquid secretion; and 3, clear liquid secretion. Then, three meibomian gland parameters were assessed: meibomian gland yielding secretion score (MGYSS) (range: 0-45), which was defined as the sum of the grades for all 15 glands, meibomian gland yielding clear secretion (MGYCS) (range: 0-15) and meibomian gland yielding liquid secretion (MGYLS) (range: 0-15).

## 2.4 Combined treatment with MBE, IPL and MGX

MBE was performed using the yokefellow instrument (Youke Electronic Corporation, Guangzhou, China), which contains a handpiece with a 1.80 mm diameter medical-grade diamond bur. To ensure a well-tolerated procedure, topical application of 0.1% tetracaine hydrochloride and 0.4% oxybuprocaine hydrochloride was applied. After placing topical anesthetic, a corneal shield was used to protect the ocular surface and a jojoba anesthetic ointment (JAO) (O´Brien Pharmacy, Kansas City, USA) containing 8% lidocaine and 25% jojoba wax were place on the lid margin. Patients underwent MBE on the upper and lower lid margin of both eyes at 500 rpm until complete removal of accumulated biofilm debris, epithelial keratinization or

capped meibomian glands. MBE was carried out only in the first combined treatment session. Immediately after MBE, JAO was cleaned with a cotton swab and IPL was performed.

IPL treatment was carried out with Thermaeye Plus (MDS Medical Technologies SL, Barcelona, Spain). The procedure began by applying an ultrasound gel (Carmado SL, Alicante, Spain) to the patient's periocular areas and upper eyelids. In the periocular areas, 6 light pulses were applied; 4 light pulses on the skin below the lower eyelid (with handpiece placed horizontally in the first pass and vertically in the second pass) and 2 light pulses on the canthal area (with handpiece placed vertically in first and second pass). The parameters were as follows: (1) Filter: 650 nm; (2) fluence: 9 j/cm$^2$; (3) pulses: 2; (4) duration: 3 ms; (5) Delay: 20 ms; and (6) Cooling: 70%. In the upper eyelids, 4 light pulses were applied; 2 light pulses in the first and second pass, respectively. The parameters were as follows: (1) Filter: 650 nm; (2) Fluence: 5 j/cm2; (3) pulses: 1; (4) duration: 3 ms and (5) Cooling: 70%. Fitzpatrick skin typing [28] was assessed prior to IPL treatment.

Finally, the MGX was realized on both upper and lower eyelids of each eye with a Collins forceps (Medi Instrument Inc, New York, USA). After first combined treatment session, patients were instructed to apply 0.5% dexamethasone sodium phosphate and 1% chloramphenicol topically twice a day during the first week and once a day during the second week. White Sun protection cream was recommended for the first 48 hours in the IPL treatment area.

**2.6 Statistical analysis**

Statistical analyses were performed with SPSS statistics software, version 26.0 (IBM Corporation, Armonk, NY, USA). The sample size was estimated using the GRANMO calculator, version 7.12 (Municipal Institute of Medical Research, Barcelona, Spain). It was calculated on the basis of assumed mean differences in F-NIBUT and MGYSS between the treatment and control groups at 2 months after the treatment onset, with values of 3.04 ± 3.86 and 19.75 ± 5.45, respectively. These assumed differences were based on the findings of a pilot study with 16 eyes of 8 patients in each group. With these assumptions, a sample size of 26 eyes per group would yield a power > 80% and a statistically significant paired difference of 95% confidence. Continuous variables were displayed as the mean ± standard deviation (SD) with interquartile ranges [IQRs], while ordinal categorical variables were expressed as frequencies (n) and percentages (%). After testing for normality and homogeneity of variance, the paired Student's *t*-test (parametric) or Wilcoxon's signed-rank test (nonparametric) was performed to compare intra-group clinical

outcomes. Within each group, the increment (Δ) was calculated. It was defined as the change from the last visit (LV) to baseline (B) "Δ = LV – B". Inter-group clinical outcomes, were analyzed with the unpaired Student's *t*-test (parametric) or Mann-Whitney's U test (nonparametric). Between each group, the differences were calculated as "$\Delta_{Treatment\ group} - \Delta_{Control\ group}$". The Pearson's (parametric) or Spearman's Rho correlation coefficient (nonparametric) was used to analyze the correlations between the variables. Stepwise multiple linear regression analysis was performed to detect the influential factors in dry eye symptoms (ΔOSDI and ΔSANDE). In addition, One-Way ANOVA (parametric) was performed to determine if there were statistically significant differences in ΔMGYSS according to baseline L-MGD-grade. A post hoc analysis by Bonferroni's test was carried out to determine statistically significant differences between baseline L-MGD grade. The level of significance was $P < 0.05$ for all of the comparisons.

## References


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