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DOCTORAL THESIS

**EVALUATION OF TEAR FILM STABILITY AND MEIBOMIAN
GLANDS FUNCTIONALITY AFTER MULTI-SESSION IPL
TREATMENT**

ABSTRACT

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ABSTRACT

1.Introduction

Dry eye disease (DED) represents a multifactorial disease with a globally increasing prevalence, aspect that raises the need for multiple treatment plans, individualised for every patient. This condition has a significant impact on the visual acuity of the patient and also on the ocular comfort, affecting the quality of life and consequently reaching the level of a global health issue. The raising number of pathologies associated with DED development and also the long list of risk factors already internationally acknowledged underline the great need for new treatment therapies to counteract the disease progression.

Aspects that trigger the need for a serious approach of this pathology are listed below:

- It is a chronic disease, with a mixture of worse periods with intense symptomatology and better periods of time with milder symptomatology that affect the performance of the patient in any domain of his life. One of the treatment target is to reduce the frequency of the period changing and try to bring the patient in a stable faze, as much as possible.
- Being a chronic disease, implies a chronic treatment, raising issues regarding patient compliance and the need for establishing the most non-invasive and easy to perform treatment strategy for every patient. Therapies that offer good results for a longer period of time with less effort are the most appreciated nowadays.
- Being a multifactorial disease means that in each case there are more factors leading to tear film destabilization, through various mechanisms, and novel therapies need to approach multiple changes in tear film structure and function, from different perspectives, but in the same time, in order to be effective.
- The increasing incidence among younger people.
- Danger of irreversible changes developing fast, if left untreated

Due to the fact that most cases of DED are related to MGD, novel therapies target the improvement of meibomian gland function and also the prevention of glands atrophy or appearance of irreversible changes. One of the most interesting therapy regarding way of approach, effects and results that have already been published, is the intense pulsed light treatment (IPL). This therapy gathered a lot of attention in the last 10 years, as a possible main treatment for DED related to MGD. The underlying idea of IPL therapy is its capacity to administer wide-ranging light pulses to specific locations, causing targeted photothermal damage to abnormal blood vessels and inflammatory structures while minimizing harm to nearby tissues. This approach not only targets the fundamental vascular and inflammatory factors of MGD, but also facilitates the restoration of normal meibomian gland function, thus returning the ocular surface environment to its normal state.

To sum up, IPL treatment has already proved to have following direct effects:

- Meibum liquefaction - by its photothermal effect, raising the temperature, it makes meibum much softer and with a lower viscosity
- Changing the meibomian glands microstructure
- Blocks the inflammatory reaction - by inhibiting pro-inflammatory factors and blocking the immune cell activation
- Demodex mites' eradication
- Neurotrophic effect
- Photo-modulation
- Metalloproteinases' inhibition - proteins known to have a role in dry eye disease pathogenesis

Several studies have already proven the efficiency of this treatment in general. Nevertheless, a much into detail view of the tear film dynamics during and after IPL multi-session treatment was lacking.

Our study comes to reveal all the changes that occur concerning tear film not only during IPL sessions, but also afterwards, during a 12 months follow-up period. We have decided to conduct this study in order to be able to give a complex perspective over the tear film dynamics,

by observing several parameters from different fields regarding tear film. We decided to offer detailed information about tear film stability, tear film quantity and also evaluate the ocular surface from the inflammatory perspective. Moreover, we also monitored changes in symptomatology, from a subjective point of view.

2.Study objectives

- Thoroughly examining changes in tear film stability and ocular surface health over multiple IPL therapy sessions in patients with DED and systematically analyze the acute response of the ocular surface to the therapy.
- Assessing the long-term efficacy of the treatment during three subsequent visits at 3,6,12 months after completion of the IPL treatment, yielding valuable information on its long-term effects and stability in time.
- Building a general overview regarding changes in tear film dynamics during first year of monitorization after IPL treatment completion, judging from the initial severity of symptoms and assessment outcomes.
- Providing an accurate counselling for patients regarding expectations before beginning IPL treatment.
- Assessing whether IPL treatment combined with artificial tears and heated eye mask is more efficient over time than IPL treatment combined only with artificial tears.

3.General research methodology

This study was designed as a non-randomized and retrospective cohort study. With a singular clinical setting framework, this study was conducted at the Professor Munteanu Mihnea Eye Clinic in Timisoara, Romania, from May 2021 to May 2023.

The research procedure obtained ethical approval from the Ethics Committee of the Victor Babes University of Medicine and Pharmacy Timisoara, as evidenced by record number 48/2021. The study was done in accordance with the principles outlined in the Declaration of Helsinki, which ensured ethical integrity and respect for the rights of participants. All participants were digitally provided with informed permission, which included a comprehensive and transparent explanation

of the study's objectives, procedures, and the utilization of clinical data for academic publication. This ensured that the research adhered to the highest ethical standards.

A total of 110 patients, including 220 eyes, were assessed in the study. The study included adult patients who were diagnosed with symptomatic Meibomian Gland Dysfunction (MGD) and received Intense Pulsed Light (IPL) therapy at the clinic during the stipulated study period.

Patients with following inclusion criteria were studied: patients 18 years old and above; patients diagnosed with evaporative dry eye disease correlated with meibomian gland dysfunction; patients with present symptomatology; patients already under topical treatment with artificial tears, combined or not with heated eye mask, unmodified during last 6 months prior to inclusion in the study; patients who underwent complete 4 session IPL treatment and follow-ups during first year after treatment completion.

Patients with following exclusion criteria were studied: patients with systemic disorders demonstrated to have an impact on tear film stability (Sjogren disease, thyroid pathologies, several autoimmune pathologies, skin pathologies); patients with any ocular surgery experienced within the last 3 months; patients with any ocular inflammatory episodes (keratitis, uveitis, episcleritis) within the last 6 months; patients with diagnosed glaucoma; patients with modified treatment for dry eye disease during last 6 months before IPL treatment or during the first year of monitorization.

Prior to commencing the IPL therapy sessions, participants had a thorough assessment to determine their existing level of visual comfort and to examine any possible alterations in ocular health and also an assessment was necessary to precisely customize the IPL treatment parameters. The IPL therapy was applied with a wavelength range of 500–1200 nm and a fluence of 13 J/cm². TearStim® technology (ESW Vision, Houdan, France) was chosen, due to its easy-to-use protocol and non-invasive approach and also with a high-safety profile.

IPL sessions were conducted, according to protocol, on day 1, 15, 45 and on day 75, with reassessment at 3 months, 6 months and 12 months after the assessment done after the end of the 4 sessions-treatment.

Ocular surface assessment has been provided by two different devices, first Tearcheck device (ESWvision, Houdan, France) and Schwind Sirius corneal pachymetry and topography device (SCHWIND eye-tech-solutions GmbH, Kleinostheim, Germany).

A questionnaire, EFT (Eye Fitness Test), was used to grade the severity of symptomatology. Eye Fitness Test (EFT) was conducted to subjectively evaluate general well-being and eye fitness. Scores between 35-44 reveal a normal tear film state, meanwhile scores between 29-35 reveal a mild form of dry eye disease and between 24-29 a moderate form of dry eye disease. Moreover, scores under 24 underline the existence of a severe form of DED.

For analyzing tear film stability, following parameters have been studied: NIFBUT (non-invasive first break up time), NIABUT (non-invasive average break up time), TFSE (tear film stability evaluation). The SCHWIND SIRIUS device projected a sequence of concentric rings onto the cornea and took detailed images to identify the initial rupture in the tear film. The initial occurrence of the first break was documented as the NIFBUT. The means/duration of these break-ups was computed and documented as the NIABUT. Values under 2 seconds are considered part of a severe dry eye disease form, between 2-5,9 seconds as a moderate dry eye disease form, between 6-10 seconds a mild form of dry eye disease and over 10 seconds as an unaffected eye. TFSE is a direct procedure for reflecting tear film instability, by assessing the tear film surface regarding appearing micro-deformations. During a 10s imaging period, number and intensity of these micro-deformations is recorded, classifying patients into four categories assigned with score points.

Tear film volume was quantified using CTMH (central tear meniscus height) and TTMH (thickest tear meniscus height), evaluated with TearCheck device. The process entailed quantifying the tear meniscus height by initially instilling fluorescein dye into the eye to highlight the tear film. The device subsequently acquired high-resolution photos and employed automated algorithms to identify and quantify the height of the tear meniscus based on these images.

Ocular surface inflammatory evaluation (OSIE) is a quantitative assessment conducted 120 seconds after the application of fluorescein dye. Normally, the dye should be cleared from the ocular surface within this time frame. However, in the presence of inflammation, the dye persists on the ocular surface for an extended duration due to its adherence to the corneal and conjunctival changes caused by inflammation. The result of this measurement is expressed as a percentage,

low values being linked to better results. A result under 10% is considered normal, between 10-25% with a mild DED, between 25-40% with a moderate DED and all the results over 40% are linked to severe DED.

4.Results

4.1. First response of the ocular surface to the IPL treatment

- A statistically significant increase in EFT mean score ($p<0.01$) is registered in each measurement, comparatively with previous one, result indicating a relevant improvement in symptomatology. Significant result were noticed even after the first IPL session. The notable increase is starting from an average value of 29.10 ± 8.87 SD in score points and raises up until an average value of 35.91 ± 7.03 SD in score points.
- First break-up time (NIFBUT) improves significantly from early stages of IPL treatment (from an average value of 9.37 ± 6.04 SD in seconds to 11.24 ± 5.60 SD in seconds), change that remains persistent during IPL sessions. Average break-up time (NIABUT) improves significantly in the late stages of IPL treatment (from an average of 11.07 ± 4.98 SD in seconds to 12.34 ± 4.66 SD in seconds)
- TFSE, with a normal range under 200 score points, starts from higher average value of 337.78 score points with a large standard deviation of ± 414.08 , going until lower mean values of 206.02 score points and a much more limited standard deviation of ± 240.44 . These changes clearly show a higher stability of the tear film as a prompt response of the IPL treatment.
- During times of assessment, a statistically insignificant change has been registered, with p-values >0.05 , regarding quantitative parameters
- Small steps of inflammatory regression are registered between measurements, with no statistically significant differences ($p=0.11$ both between time 1 and 2 of measuring and between time 2 and time 3 of measuring). Nevertheless, from an overall perspective, comparing the beginning of the treatment with the result at the last measurement, significant changes are found ($p<0.01$). The percentage of inflammation registered a significant decrease from an average value of 7.26 ± 7.86 SD until an average value of 5.05 ± 4.77 SD

4.2. Long-time response of the ocular surface to the IPL treatment

- Statistically significant differences were registered between all follow-ups ($p < 0.01$), with mean values raising from 34.0 ± 12.0 SD (baseline) to 42.0 ± 4.0 SD (12 months) in score points. The highest raise in score was registered from baseline to 3 months follow-up, from a mean value of 34.0 ± 12.0 SD until 40.0 ± 7.0 SD. This score improvements is impressive in comparison to dynamics registered between 3 and 6 months or between 6 and 12 months. Symptomatology continues to improve even after IPL treatment completion, more in the first months, and with smaller steps afterwards, but still significant.
- Significant improvements ($p < 0.01$) were observed in the NIFBUT and NIABUT measures, indicating a positive outcome in terms of tear film stability. Mean values start from 7.40 ± 12.67 SD in seconds (NIFBUT) and 10.70 ± 9.38 SD in seconds (NIABUT) at baseline, improve at 17 seconds until 3 months follow up and maintain the result even at 12 months follow up, with a smaller range.
- Good score points are registered regarding TFSE even from the baseline, with not significant improvements in the first 6 months, only afterwards.
- Mean CTMH was significantly lower (under 0.40 mm) during follow-up period in comparison to values registered during IPL sessions (0.44 mm). Same results were registered when analyzing TTMH, with values over 0.50 mm during IPL sessions and values under 0.40 mm during follow-up period. Overall, regarding quantitative parameters, no significant changes have been registered during the follow-up period.
- Statistically significant decrease ($p < 0.01$) is registered from a follow-up to another regarding OSIE, quite constant but with a significant range, showing that inflammatory response of the ocular surface decreases slowly and in a constant manner and it is a parameter difficult to control.

4.3. Comparison of IPL treatment effects between patients being treated only with artificial tears as an additional treatment and those treated also with eye thermal mask

For achieving the secondary objectives, the entire lot of patients was split in two groups. First one, named the control group, was considered the one with patients undergoing IPL treatment with topical additional treatment, unmodified 3 months before beginning of the treatment and 12 months afterwards. Study group 2, named thermal mask group, represented patients who started

and completed IPL treatment, and underwent all follow-up measurements, meanwhile using a Posiforlid thermal mask every day, as an additional treatment besides artificial tears.

Study group 1, also known as the control group, consisted of 73 patients, which included a total of 146 eyes. In contrast, study group 2, named thermal mask group, comprised 37 patients, with a total of 74 eyes. In our study, the average age for the control group was 54.31 years, whereas for the IPL and heated eye mask group, it was 47.08 years, quite similar between and relevant in comparison.

Same parameters have been analyzed, during same assessment moments, and the results between IPL sessions are presented in table 12 and the ones during follow-up period are presented in table 13.

There was no significant increase in improvement observed in the examined parameters during and after IPL multi-session therapy when paired with the use of a thermal mask.

5.Discussion and conclusions

The study's findings demonstrate a gradual enhancement in the treatment of DED during undergoing IPL therapy sessions and even in the first year of observation afterwards.

Individuals encountered a consistent alleviation in their symptoms as a direct result of the IPL sessions, and also as a long-term effect after completing the IPL treatment. There is a noticeable rise in the stability of the tear film, demonstrated by enhancements in both the non-invasive first breakup time (NIFBUT) and non-invasive average break-up time (NIABUT), indicating a more stable and unified tear layer.

The surface assessment, particularly the Ocular Surface Inflammation Evaluation (OSIE), revealed a reduction in the percentage of inflammation, indicating a substantial drop in ocular surface inflammation from the beginning to the end of the therapy session, decrease that continued during the first 12 months of evaluation. The consistent capture time of OSIE across the sessions suggests a uniformity in the evaluation process and the relevance of the results.

Although there were improvements in tear film stability and surface quality, the amount of tear film, as evaluated by CTMH and TTMH, did not improve during the sessions. These findings

indicate that IPL therapy has a positive impact on the quality of tear film, but does not have any influence on its amount.

Our study fortifies the connection between IPL and DED symptomatology improvements and goes forward by demonstrating the stability of the effect in time, showing an improvement in symptomatology not only during IPL sessions but also afterwards, even during the first year of monitorization. We presume that due to the fact that improvements could be registered 12 months after the completion of the treatment, keeping the obtained results will last much longer. Authors revealed possible connections between the symptom relief and changes in visual acuity, aspect that we did not approach in our study. Nevertheless, several studies regarding persistence in time of the improved symptomatology and also connections between this effect and improvement or not in visual acuity should be made.

Just as other studies already have proven, IPL treatment has a positive effect on tear film stability. We also managed to demonstrate the fact that a slower but significant improvement is seen during the IPL sessions and a much considerable improvement is seen after first months of treatment completion, suggesting the fact that stability of tear film comes slowly in time and also reinforcing the idea of cumulative effect of the IPL sessions.

The decrease in inflammation on the surface of the eye, as observed in the data, is consistent with the findings reported in reducing the signs and symptoms of dry eye disease (DED). This convergence highlights the therapeutic significance of targeting both symptomatic alleviation and the underlying inflammatory processes associated with Dry Eye Disease (DED) caused by Meibomian Gland Dysfunction (MGD). The inflammation decrease is quite constant during the IPL sessions and follow-up periods with no difference in dynamics between the two main study periods.

IPL treatment proved efficient in registering a good outcome in studied parameters, no matter the beginning severity of the ocular surface state. Our study outcomes show stable and best improved results in several studied parameters, despite of high variety of disease levels in the beginning.

Conducted studies emphasize technological improvements and comparisons of novel devices in the field of IPL therapy. Their investigation of advanced IPL equipment and the integration of IPL with photo-biomodulation therapies provides valuable understanding of the ongoing advancement

of IPL technology. The advancement in device innovation and treatment methodology corresponds with the implications of our study, which suggest continuous improvement in the effectiveness of IPL therapy and the outcomes for patients.

The inquiry of the prolonged effectiveness of the supplementary Posiforlid heated eye-mask therapy was also brought up in our study. After evaluating the patient's quality of life and also objective parameters regarding inflammation and stability of the tear film, we determined that the study showed a result that was not statistically significant between the two groups. This result may influence patients to choose a 4-session IPL therapy with a single session repetition every 3-6 months, rather than using a heated eye mask every day. The initial approach is more efficient in terms of time, although being more costly. Moreover, others proved in their study that the IPL was more effective in enhancing the long-term stability of the tear film compared to a heated eye mask, which demonstrated efficacy only for a brief duration. Still, other writings proved that combined heated mask with IPL is much more efficient than IPL alone, although these studies were conducted with only 3 sessions and only 3 months of monitoring after treatment completion and presented an average age of less than 30 years old, in comparison with our study average.

The need for further studies regarding combined therapies and a more complex approach in treating DED remains viable.

When recommending IPL therapy for DED management, it is crucial to take into account the unique characteristics and preferences of each patient in order to provide an individualized approach in clinical practice. As the amount of data expands and treatment procedures become more precise, IPL therapy is being considered to have a progressively important impact on enhancing the quality of life for patients with Dry Eye Disease (DED) caused by Meibomian Gland Dysfunction (MGD).

