Pulsed light therapy for the treatment of dry eyes: retrospective analysis of a series of cases

Terapia de luz pulsada para tratamento de olho seco: análise retrospectiva de uma série de casos

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ABSTRACT

Objective: To evaluate the immediate effectiveness of intense regulated pulsed light applied to the periocular area of patients with dry eyes in a retrospective study of a series of cases.

Methods: Seventy-six participants underwent intense regulated pulsed light therapy, consisting of light pulses applied to both periocular areas. In addition to a comprehensive ophthalmological examination, tear osmolarity measurements were taken for both eyes. Participants were also administered the Ocular Surface Disease Index (OSDI) questionnaire. Data were collected at baseline and 30 days after the final session of intense regulated pulsed light treatment for comparative analysis.

Results: A statistically significant difference was observed between the mean OsmoOD/OSPre and the mean OsmoOD/OSPost30. Furthermore, a highly significant difference was found between OSDIPre and OSDIPost30.

Conclusion: Intense regulated pulsed light therapy effectively improved both objective tear osmolarity measurements and the subjective response to the OSDI-IDSO questionnaire in patients with DED over the observed period.

RESUMO

Objetivo: Avaliar a efetividade da luz pulsada regulada de alta intensidade aplicada na área periocular de pacientes com olho seco em estudo retrospectivo de série de casos.

Métodos: Foram submetidos à terapia com luz pulsada regulada de alta intensidade 76 participantes, com os pulsos de luz aplicados às suas áreas perioculares. Além do exame oftalmológico básico, a osmolaridade lacrimal foi medida em ambos os olhos, e os participantes foram estimulados a responder ao questionário *Ocular Surface Disease Index* (OSDI), com os dados da avaliação inicial comparados aos do 30° dia após a última sessão.

Resultados: Ocorreu diferença significativa entre a média do OsmoOD/OSPre e a média OsmoOD/OSPost30. Também houve diferença significativa entre a resposta ao questionário OSDIPre e ODIPost30.

Conclusão: A luz pulsada regulada de alta intensidade foi eficaz ao melhorar tanto as medidas objetivas de osmolaridade quanto a avaliação subjetiva das respostas ao questionário OSDI de pacientes com olho seco no período observado.

INTRODUCTION

The term "dry eye" can be defined as a multifactorial disorder of the tear film and ocular surface, leading to symptoms of discomfort, visual disturbances, and tear film instability, with potential harm to the ocular surface.[1] It is an extremely common condition resulting from alterations in tear volume or function, which can trigger various ocular changes.[2] The tear film comprises three layers: the lipid layer, secreted by the meibomian glands, primarily serving to prevent the evaporation of the aqueous layer and maintain the tear film's thickness; the aqueous layer, secreted by lacrimal glands, responsible for providing oxygen to the corneal epithelium and enhancing its optical properties; and the mucin layer, mainly secreted by conjunctival goblet cells, responsible for corneal lubrication.[2]

According to the Subcommittee of the International Dry Eye Workshop 2007 (DEWS), dry eye can be classified into aqueous-deficient dry eye or evaporative dry eye. In the first group, T-cell-mediated dysfunction in the lacrimal gland leads to decreased tear production and the spread of inflammatory mediators on the ocular surface. In the latter, dysfunction of the meibomian gland (meibomian gland dysfunction – MGD) is characterized by altered lipid metabolism, resulting in the transition of unsaturated fats to saturated fats, causing tear film instability, tear evaporation, and subsequent tear hyperosmolarity.[1] Epidemiological data indicate that the prevalence of this disease increases with age, affecting approximately 10% of individuals between 30 and 60 years and 15% of adults over 65 years old.[1] Additionally, it is more common in females and among individuals of Asian descent.[3] About 30% of the patients may have an association of the two main groups, exhibiting signs of both groups in a so-called "mixed form".[2,3]

The diagnosis of various forms of dry eye encompasses simple examinations to be conducted under slit-lamp microscopy, such as tear film breakup time (TBUT), the use of dyes, observation of superficial keratitis and a comprehensive assessment of the ocular surface, along with the administration of the subjective Ocular Surface Disease Index (OSDI) questionnaire.[4] More recently, the measurement of tear osmolarity has been introduced as a novel parameter for assessment[5] and became part of the definition of dry eye according to Tear Film Ocular Society (TFOS) since 2017.[6]

Other technological assessments of diagnosis are available by the use of the ocular aberrometer (Topcon KR1W), as it can provide after ten consecutive aberrometries, changes by degradation of the image quality reflecting the status of the tear film of a subject. Several multi-tasking machines like, for example, the Keratograph 5M (Oculus, Germany) or the Tearcheck® (E-Swin, France), can provide valuable information such as non-invasive TBUT, meibography, meniscus height, bulbar redness level, among others. They are particularly useful when the traditional methods fail at slit lamp observation.[7]

The treatment of this condition involves artificial tears, warm compresses, meibomian gland expression (depending on the pathophysiological mechanism underlying the disease), omega-3 supplementation, topical/oral antibiotics, topical corticosteroids, and/or topical cyclosporine.[8] Intense pulsed light (IPL) has been applied in the periocular region for over a decade for the dermatological treatment of excessive periorbital pigmentation and erythematotelangiectatic rosacea.[9,10]

Following reports of improvement in dry eye symptoms in some patients with rosacea and ocular surface disease after IPL treatment, the use of IPL devices was expanded to include treatment for evaporative dry eye associated with MGD.[9] The technique was then adapted to target not the skin but the meibomian glands, giving rise to intense regulated pulsed light (IRPL) therapy, which has already demonstrated positive outcomes in managing evaporative dry eye.[11] Other technologies, like Lipiflow (J&J USA) /iLlux (Alcon/USA) performs automated warm massages and are also part of the Dry-eyes arsenal, but their performances are not part of this study.[12]

The objective of this study was to evaluate the effectiveness of IRPL therapy applied to the periocular area of dry eye patients, whether associated with MGD or not, and to present the subjective (OSDI) and objective (physical examination and osmolarity test) findings at the conclusion of treatment. To accomplish this, a retrospective case series study was conducted involving 76 patients previously diagnosed with dry eye and exhibiting unsatisfactory responses to various prior clinical treatments.

METHODS

Study design

This was a retrospective observational case series conducted between May 2016 and June 2020 at the Instituto de Olhos de Minas Gerais, Belo Horizonte (MG, Brazil). The study included individuals with lacrimal dysfunction, encompassing both dry eye disease (DED) and MGD, who were eligible for IRPL therapy. Both patients were covered with evaporative dry eye, as well as those with aqueous

deficiency because, even if to a lesser extent, they could also benefit from therapy. The research protocol received ethical approval from the Research Ethics Board of the Universidade Nilton Lins/Research Ethics Committee (CEP) in Manaus (AM, Brazil), and adhered to the principles of the Helsinki Declaration. All patients provided written informed consent for their participation.

Seventy-six (n = 76) participants underwent IRPL therapy with sequenced light pulses administered to both periocular areas at intervals of the first, 15th, 45th, and 75th days following the initial assessment. In addition to a basic ophthalmological examination, tear osmolarity was meticulously measured in both eyes (OsmoOD/OsmoOS). Patients were encouraged to respond to the OSDI questionnaire, which had been translated and validated for the Portuguese language (OSDI-IDSO)[13]. These data were compared at the outset, prior to the initiation of pulsed light treatment (OsmoODPre/OsmoOSPre/OSDIPre), and 30 days after the final IRPL session (OsmoODPost30/OsmoOSPost30/OSDIPost30). Slit lamp evaluation associated with the application of the OSDI questionnaire and the assessment of tear osmolarity are easy, quick, and accessible measures for clinical evaluation of the tear film. Furthermore, in 2017, osmolarity assessment became part of the definition of dry eye according to TFOS.[6] For this reason, this objective assessment was prioritized.

Participants

Individuals with documented lacrimal dysfunction of both sexes, exhibiting varying degrees of dry eye in its diverse presentations, without distinction based on the pathophysiological mechanisms leading to its development were included in the study. Patients with both evaporative dry eye and aqueous-deficient or mixed forms were considered. All participants had previously undergone clinical treatment but exhibited partial treatment failure**.** It was decided to maintain clinical treatment during IRPL treatment in order to act as an adjuvant therapy to the new treatment instituted. At the end of the sessions, some patients were able to reduce the topical therapy used, while others maintained the same dosage. Exclusion criteria encompassed prior ocular surgery, pregnancy or breastfeeding, corneal degenerations, ocular allergies, the use of anti-glaucomatous drops and other ocular diseases that might influence ophthalmological examination. Skin abnormalities in the periocular area were also excluded. Individuals with significant comorbidities, such as diabetes and collagen-related diseases, were excluded as well. The diagnosis of dry eye was based on medical history, objective ophthalmological examination, and the assessment of osmolarity for each patient.

Ocular surface assessments

Responses from the OSDI/IDSO were collected, and osmolarity was measured at the beginning of the study and 30 days after the last IRPL treatment session. Additionally, an examination with TearChek® diagnostic tool (E-Swin, Roudan, France) was conducted as a complimentary source of tear film data to better assess dry eye. Osmolarity was assessed separately for each eye.

The subjective parameter OSDI is a survey of dry eye symptoms, and participants responded after a brief explanation. The questionnaire serves as a valuable tool for the subjective assessment of dry eye symptoms. It consists of 12 questions rated from zero to four, with a maximum score of one hundred, where higher scores indicate more severe symptoms. The total value is calculated by summing the scores, multiplying it by 25, and then dividing by the number of answered questions.[10,11] The questionnaire was translated and validated, and in the Portuguese language it is known as IDSO.[11]

The objective parameter of osmolarity quantification was carefully assessed by a single investigator to reduce variability, as it is an important global marker used in dry eye investigation.[5] The I-Pen® Tear Osmolarity System (I-Med Pharma, Dollard-des-Ormeaux, QC, Canada) was used for this purpose, with the device's single-use sensor tip gently touching the accumulated tear film on the outer part (conjunctival sac) of each eye[14]. Reference values for this method are: < 290 mOsm/L = normal; 290 to 310 = marginal/at risk; 310 to 330 = mild dry eye; 330 to 350 = moderate dry eye; > 350 = severe dry eye; a difference of 8 or more between eyes indicates dry eye.

The I-Pen® is a portable osmolarity system that uses electrical impedance amplitude and must be placed at an angle of 30 to 45° on the patient's lower tarsal conjunctiva, providing a tear osmolarity reading within a few seconds of starting the measurement.[15]. In 2018, Chan et al. conducted a study that tested in vitro the validity and reliability of this new system and demonstrated that the portable instrument represents a fast, accurate, and reproducible method for measuring tear osmolarity, thus allowing us to conclude that, if used according to the manufacturer's standards *in vivo*, can also provide extremely superficial and consistent results[14]. Previously, in 2016, Jiang et al. had already demonstrated the effectiveness of using E-Eye in a study carried out with 40 eyes in China[16].

Figure 1. Application of pulsed light to the area of skin just below the lower eyelid.

Intense regulated pulsed light treatment

The IRPL treatment (E-Eye IRPL®, E-Swin, Houdan, France) was administered over a 75-day protocol period, with flashes directed to the skin area immediately below the lower eyelid during four sessions, without the need for additional sessions. Five pulses were applied with an intensity ranging from 9 to 13 J/cm, inversely proportional to the skin phototype level, as determined by the Fitzpatrick grading scale.[17] Lighter skin types required the use of stronger power settings, while very dark skin types were often considered contraindicated for IRPL treatment due to unresponsiveness.[17] Both eyes received treatment while protected by opaque eyewear (Figure 1).

Intense regulated pulsed light must be employed at right intervals, and all participants were able to follow the protocol flawlessly. Not doing this must compromise the results, and also due its cumulative properties, better results would be noticeable after three or four sessions. Unlike the dermatologic procedures for different pathologies, the IRPL are considered by most patients as a very comfortable and fast treatment. All four sessions of all the patients in this study were performed by only one experienced technician following the Fitzpatrick skin color grade to better choose the pulse intensity but in most cases it not necessary to reduce power settings.

Statistical analysis

All data were organized in Microsoft Excel 4® (Microsoft Corporation, Redmond, WA, USA), and following a critical examination of the observations, a total of 76 patients (n = 76) were included in this study. Quantitative variables are presented in tables with statistical measures (mean, standard deviation, minimum, maximum, among others), while qualitative variables are presented in frequency distribution tables (frequency and proportion). The paired Student's t-test was used to compare osmolarity and OSDI before and after treatment. Calculations were performed using the Minitab Statistical Package® 2020 (Minitab Inc., State College, PA, USA), and values of $p < 0.05$ indicated statistical significance.

RESULTS

A total of 76 individuals were assessed, comprising 54 females (71.05%). The mean ± standard deviation of age was 60.9 ± 17.5 years (range: 26 to 85 years; median: 64.0 years). Table 1 shows the osmolarity in each eye before and after 30 days of treatment according to the age group of the patients.

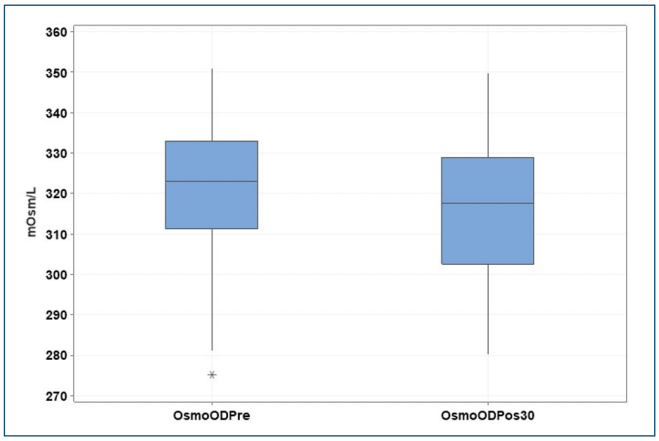
For the right eye (RE), there was a significant difference (p-value = 0.015) between the mean tear osmolarity pre-treatment (OsmoODPre) and the mean tear osmolarity 30 days post-treatment (OsmoODPost30), as shown in figure 2 and table 2.

For the left eye (OS), there was a significant difference (p-value = 0.017) between the mean tear osmolarity pre-treatment (OsmoOSPre) and the mean tear osmolarity 30 days post-treatment (OsmoOSPost30), as shown in figure 3 and table 3.

Table 1. Osmolarity before and after 30 days of treatment in each age group

Variable	n	Meaning	Standard deviation	Minimum	First trimester	Median	Third trimester	Maximum
Age	76	59.78	16.92	26.00	50.00	64.00	74.00	85.00
OsmoODPre	76	321.57	17.34	275.00	311.25	323.00	333.00	351.00
OsmoODPos30	76	315.92	17.61	280.00	302.50	317.50	329.00	350.00
OsmoOSPre	76	321.49	22.98	190.00	308.00	324.50	333.75	361.00
OsmoOSPos30	76	316.32	17.15	278.00	306.00	319.00	328.75	357.00
OSDIPre	76	59.48	23.75	10.00	40.10	57.63	76.50	100.00
OSDIPos30	76	38.60	25.38	0.00	18.75	32.29	57.19	100.00

OsmoODPre: tear osmolarity in the right eye at the beginning of the study; OsmoODPos30: tear osmolarity in the right eye 30 days after treatment; OsmoOSPre: tear osmolarity in the left eye at the start of the study; OsmoOSPos30: tear osmolarity in the left eye 30 days after treatment; OSDIPre: Ocular Surface Disease Index at baseline; OSDIPos30: Ocular Surface Disease Index 30 days after treatment.



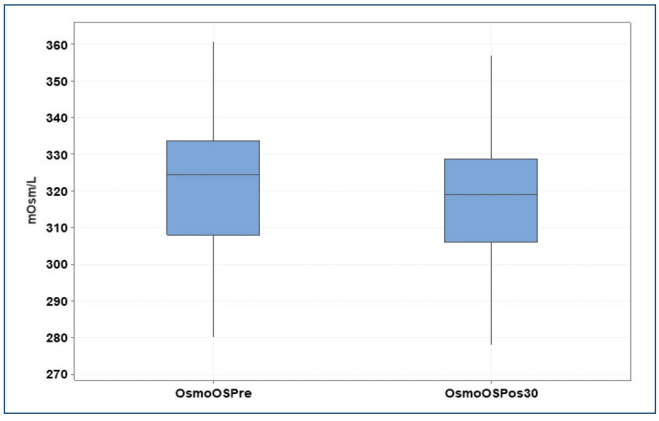
OsmoODPre: tear osmolarity in the right eye at the beginning of the study; OsmoODPos30: tear osmolarity in the right eye 30 days after treatment.

Figure 2. Mean tear osmolarity pre-treatment and after 30 days of treatment in the right eye.

Table 2. Tear osmolarity in the right eye at baseline and after 30 days of treatment

Variable	N	Meaning	Standard deviation	p-value
OsmoODPre	76	321.57	17.34	0.015
OsmoODPos30	76	315.92	17.61	

OsmoODPre: tear osmolarity in the right eye at the beginning of the study; OsmoODPos30: tear osmolarity in the right eye 30 days after treatment.



OsmoOSPre: tear osmolarity in the left eye at the start of the study; OsmoOSPos30: tear osmolarity in the left eye 30 days after treatment.

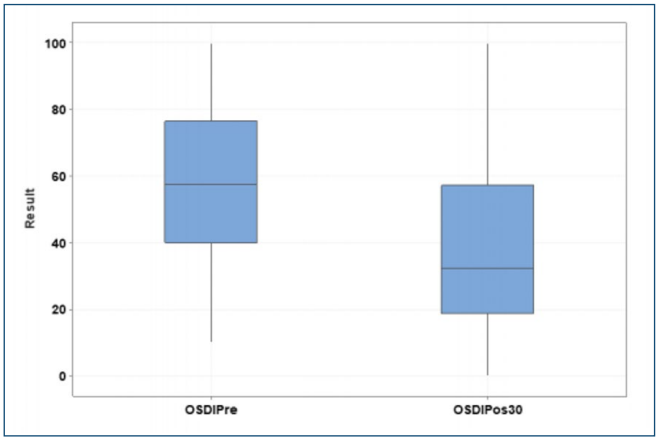
Figure 3. Mean tear osmolarity pre-treatment and after 30 days of treatment in the left eye

Table 3. Tear osmolarity in the left eye at baseline and after 30 days of treatment

Variable	N	Meaning	Standard deviation	p-value
OsmoOSPre	76	321.49	17.54	0.017
OsmoOSPos30	76	316.32	17.06	

OsmoOSPre: tear osmolarity in the left eye at the start of the study; OsmoOSPos30: tear osmolarity in the left eye 30 days after treatment.

There was a significant difference (p-value < 0.001) between OSDIPre and OSDIPost30, which means that, on average, OSDIPost30 was significantly lower than OSDIPre, as shown in figure 4 and table 4.



OSDIPre: Ocular Surface Disease Index at baseline; OSDIPos30: Ocular Surface Disease Index 30 days after treatment.

Figure 4. Results of pre-treatment Ocular Surface Disease Index variation compared to 30 days after treatment.

Table 4. Results of pre-treatment Ocular Surface Disease Index variation compared to 30 days after treatment.

Variable	N	Meaning	Standard deviation	p-value
OSDIPre	76	58.48	23.25	< 0.001
OSDIPos30	76	38.60	25.30	

OSDIPre: Ocular Surface Disease Index at baseline; OSDIPos30: Ocular Surface Disease Index 30 days after treatment.

DISCUSSION

This study demonstrated an improvement in both subjective (OSDI) and objective (osmolarity) parameters for dry eye evaluation after four sessions of IRPL treatment in patients who had previously undergone clinical interventions. IRPL is a relatively new treatment modality with limited available data regarding its efficacy. The quantification of osmolarity was chosen due to its objectivity, ability to grade disease severity as mild, moderate, or severe, and its high positive predictive value.

In 2018, Albietz et al.[9] conducted a prospective open-label study involving 26 participants to assess the effectiveness of periocular IPL therapy combined with meibomian gland expression in the treatment of chronic dry eye. The study showed significant improvements in symptoms, as measured by the OSDI questionnaire, six weeks after treatment completion. Additionally, objective parameters assessed through slit-lamp examination, including TBUT and corneal fluorescein staining, also improved. Similarly, Rong et al. [10] conducted a prospective, randomized, double-blind, controlled study involving 44 patients, demonstrating improvement in the study group in evaluation scores for meibomian gland secretion, TBUT, fluorescein staining, and subjective assessment using the OSDI (SPEED) questionnaire. In contrast, the control group showed significant improvement only in SPEED scores and fluorescein staining. In another

cohort study, Yin et al.[18] included 35 patients and showed improvements in the microstructure of the Meibomian glands, evidenced by increased acinar gland diameter and density, in contrast to the absence of structural improvement in the control group.

The study presented here contributes to the literature by demonstrating significant improvements ($p < 0.05$) in both subjective parameters, as evaluated by the patients, and objective parameters, as measured by the tear film osmolarity test, both before and 30 days after treatment completion. However, the distinctive aspect of this study lies in its ability to demonstrate such efficacy through the use of IPL, regulated with predetermined energy and spectra, designed to specifically target the Meibomian gland, while the majority of previous studies have primarily assessed the efficacy of IPL, which is already widely used in dermatology for the treatment of conditions like rosacea and telangiectasias.

Although the mechanisms of action of IPL and IRPL have not been fully elucidated, Karaca et al.[17] propose that laser application to the lower eyelid and temporal region stimulates parasympathetic branches, causing the Meibomian glands to return to their normal activity. Additionally, it is believed that local heating of the glands influences better meibum expression and reduces inflammation through the selective destruction of telangiectatic blood vessels at the eyelid margin.[18-23]

For some time, patients with darker skin were excluded from IPL and IRPL studies due to reported complications or ineffectiveness of therapy in these individuals. However, in 2021, Vergés et al.[24] included patients with varying degrees of skin pigmentation (Fitzpatrick scale types I to VI) in their analysis, revealing that there were no complications in patients with darker skin and demonstrating similar efficacy in this group compared to patients with lighter skin. Although Vergés et al.[24] having used other equipment in the development of their study, in 2020 Xue et al.[8] showed safety and efficacy when using E-Eye in patients with phototypes I to V according to the Fitzpatrick classification. For those with darker skin, the effectiveness of the E-Swin device has not yet been demonstrated.

A distinctive aspect of our study was the inclusion of individuals with different pathophysiological mechanisms for the development of dry eye. Treatment was administered to patients with both lipid-deficient dry eye and those with aqueous-deficient or mixed forms. The purpose of allocating all these patients to a single group was to make the study even more representative of patients seen in general ophthalmic practices, which often lack the ideal equipment and technology for differentiating and documenting specific dry eye types. In Belo Horizonte, for instance, the capital of Minas Gerais with a large number of ophthalmologists, there are few devices capable of providing an objective assessment that distinguishes aqueous deficiency from lipid deficiency, with most of these devices only available in specialized corneal practices and rarely used by general ophthalmologists. Consequently, the treatment of this frequently encountered condition in routine ophthalmic consultations is typically conducted without such differentiation and documentation, often by general ophthalmologists.

Another important point to emphasize is that the percentage of patients with dry eye due to a deficiency in the lipid component, combined with mixed deficiency, accounts for 85% of all individuals affected by the condition. Therefore, we believe that the results of the present study could have been even better if patients with pure aqueous deficiency had been excluded, as they are known not to respond to the therapy applied.

Although the osmolarity test is capable of classifying the disease as mild, moderate, or severe, its results were associated with subjective parameters reported by the patient to reduce potential false-negative errors in the study outcome. Nevertheless, no patients showed documented clinical improvement at the end of the treatment without an improvement in osmolarity assessment, which reinforces the reliability of using osmolarity as an evaluation parameter for dry eye and also, for the effectiveness of the equipment employed, the I-Pen® device.

We acknowledge the presence of limitations in our study for detecting the effectiveness of IRPL due to the lack of a control group and the high cost of the therapy applied. Most IRPL studies available[14,18, 20-24] report long lasting results up to one year, and some even longer. This particular study aims only to access immediate results at 1 month after treatment only, and the same patients were not further submitted to other tests to study results at long term. Nonetheless, it revealed that IRPL can be a useful, safe, and effective treatment option, considering the results presented here showing improvement in both subjective measures (questionnaire responses to assess symptom intensity) and objective measures (tear osmolarity) for dry eye treatment. However, further randomized prospective studies with control groups are needed, along with long-term treatment efficacy assessment, to determine if the improvements in symptom

signs are maintained over the long term after treatment completion.

CONCLUSIONS

The intense regulated pulsed light was effective in improving both the objective measurement of tear osmolarity and the subjective response to the Ocular Surface Disease Index-IDSO in patients with dry eye in the period observed and offers a high safety level of treatment. No side or adverse effects were observed, despite the variability in the results for each subject, as expected for such a large and leveled sample. Further studies are needed to evaluate the long-term results and propose the use of intense regulated pulsed light as a standard therapy for the condition presented.

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