ARCH SOC ESP OFTALMOL. 2019;xxx(xx):xxx–xxx

ARCHIVOS DE LA SOCIEDAD ESPAÑOLA DE OFTALMOLOGÍA

www.elsevier.es/oftalmologia

Original article

Intense pulsed light therapy: A promising complementary treatment for dry eye disease☆

L.F. Mejía[a,b,*], *J.C. Gil*[b], *M. Jaramillo*[c]

[a] *Head Cornea Service, School of Medicine, CES University, Medellín, Colombia*
[b] *Ophthalmology Research Service, School of Medicine, CES University, Medellín, Colombia*
[c] *Ophthalmology Service, School of Medicine, CES University, Medellín, Colombia*

ARTICLE INFO

Article history:
Received 26 November 2018
Accepted 15 March 2019
Available online xxx

Keywords:
Pulsed light therapy
Dry eye
Rosacea
Sjögren's syndrome
Meibomian gland dysfunction

ABSTRACT

Objective: To propose the intense pulsed light (IPL) therapy as a helpful supplementary treatment in patients with dry eye disease.

Material and methods: Retrospective cross sectional design. Medical records of patients in whom dry eye disease symptoms were not satisfactorily controlled with medical therapy alone and who underwent additional IPL therapy, and tree sessions were completed. Data were analyzed before therapy and 3 weeks after its completion to assess improvement. Determination of symptoms, through a visual analog scale; tear film stability, through tear Break Up Time (tBUT); measurement of tear secretion, through Schirmer Test; and ocular surface staining with Van Bijsterveld score were evaluated. SPSS software and nonparametric analysis of repeated measures were used. The study was approved by the ethics committee.

Results: 50 eyes from 25 subjects were reviewed. There were 9 males (36%) and 16 females (64%), with a median age of 59 years (IQR 52–64). The median of the symptoms scale was 8 (IQR 8–9) and 3 (IQR 2–4) before and after the therapy respectively ($p < 0.05$). The median of BUT was 4 (IQR 3–5) and 10 (IQR 8–11), Schirmer test was 13 (IQR 12–15) and 15 (IQR 13–20), and Van Bijsterveld score was 3 (RIC 3–4) and 2 (IQR 2–3) before and after the therapy respectively ($p < 0.05$, for all measurements).

Conclusion: IPL treatment has excellent results regarding both: dry eye disease symptoms improvement and in office objective tests such as tBUT, Schirmer test and Van Bijsterveld score; IPL could be considered as an effective adjunct for dry eye disease.

☆ Please cite this article as: Mejía LF, Gil JC, Jaramillo M. Terapia de luz pulsada intensa regulada: un tratamiento complementario prometedor para la enfermedad de ojo seco. Arch Soc Esp Oftalmol. 2019. https://doi.org/10.1016/j.oftal.2019.03.009

* *Corresponding author.*
E-mail address: lfmejia@lfmejia.com (L.F. Mejía).

Terapia de luz pulsada intensa regulada: un tratamiento complementario prometedor para la enfermedad de ojo seco

Palabras clave:
Terapia de luz pulsada
Ojo seco
Rosácea
Síndrome de Sjögren
Disfunción de glándulas de Meibomio

RESUMEN

Objetivo: Presentar los resultados del tratamiento con luz pulsada regulada (IPL) en pacientes con ojo seco.
Material y métodos: Estudio retrospectivo. Se analizaron historias clínicas de pacientes con ojo seco sometidos a terapia IPL en quienes no se logró un control satisfactorio de los síntomas luego de terapia médica. Se evaluó previo al inicio y al final de la terapia una escala analógica visual de síntomas y además el tiempo de rotura de la película lagrimal (tBUT), test de Schirmer y puntaje de Van Bijsterveld. Se realizó un análisis de medidas repetidas con SPSS comparando los resultados antes y después de realizar la terapia IPL.
Resultados: Se analizaron 50 ojos de 25 pacientes: 9 hombres (36%) y 16 mujeres (64%); se encontró una mediana de edad de 59 años (RIC 52-64). La mediana en la escala de síntomas fue de 8 (RIC 8-9) y 3 (RIC 2-4) antes y después del tratamiento con IPL ($p < 0,05$). El tBUT tuvo una mediana de 4 (RIC 3-5) y 10 (RIC 8-11), el test de Schirmer de 13 (RIC 12-15) y 15 (RIC 13-20) y el puntaje de Van Bijsterveld de 3 (RIC 3-4) y 2 (RIC 2-3) antes y después del tratamiento, respectivamente ($p < 0,05$ en todos los análisis).
Conclusiones: La terapia de IPL para el ojo seco es una excelente opción de tratamiento: muestra mejoría objetiva mediante la estabilización de la película lagrimal y tinción de superficie ocular, así como también mejoría subjetiva evidenciada en los síntomas manifestados por los pacientes.

Introduction

Dry eye is recognized as a multifactorial disease, where loss of homeostasis of the tear film is the central pathophysiological concept, and discomfort or visual disturbance are the leading symptoms[1]; with a high but variable incidence throughout the world, and with an estimated prevalence between 5% and 50% of the general population, reaching up to 75% in specific populations.[2]

It is broadly classified as aqueous deficient, evaporative, or mixed. Some years ago it was considered that up to 80% of dry eye patients were of the aqueous deficient type[3]; this concept has changed over the years and nowadays it is considered that approximately 80% of these patients are of the evaporative or mixed type.[1,4]

The current management of this disease comprises preservative free artificial tears, topical anti-inflammatories, topical Ciclosporin A, autologous serum and the insertion of silicone lacrimal punctum plugs[5] when needed. For patients with the evaporative type there are a number of additional therapeutic options oriented at improving the lipid layer of the tear film, such as oral doxycycline and oral and topical azithromycin,[6,7] tetracycline ointment,[8,9] and local therapies such as warm eyelid compresses, Meibomian glands manual expression,[10,11] and, more recently the use of intense pulsed light therapy (IPL).[5,12-19]

In 1989 Morgan Gustavson conceived for the first time the use of pulsed light as a medical therapy, and in 1990 presented the first model of such system at Stocolhm.[19] IPL was approved by the FDA in 1995 and has been used regularly in dermatology since 1996 for the treatment of several pigmented skin pathologies.[20] It involves the use of a xenon light flash with a wavelength between 400 and 1200 nm, whose target are different chromophores such as hemoglobin, melanin, and others such as water and the mitochondria.[21-24]

The first reports in ophthalmology date back to 2002[15]; thereafter several publications have appeared stating its usefulness in evaporative dry eye disease secondary to Meibomian Gland Disease[12,13,16,17,21] and even in Sjögren's Syndrome.[24] However, up to date there are no solid mechanisms of action suggested in ophthalmology.

The aim of this publication is to propose the intense pulsed light (IPL) therapy as a helpful supplementary treatment in patients with dry eye disease.

Materials and methods

Study design

A retrospective cross-sectional design and secondary source study was done. The records of patients with dry eye of evaporative or mixed type seen at a cornea outpatient clinic in Medellin/Colombia were considered, in whom there was not a satisfactory control of symptoms after using therapeutic options as artificial tears, cyclosporine, warm compress and punctual plugs, and who underwent IPL therapy and at least three sessions completed. The meibomian gland dysfunction was considered if abnormal lid morphology, abnormal glandular expressibility and glandular congestion were present. The ophthalmological record included a subjective questionnaire

through a visual analog scale and objective ocular surface tests pre and post IPL therapy.

A convenience sampling of medical records was performed, including the whole population in whom three IPL sessions were completed.

The study was approved by the ethics committee at the Ophthalmic Research Center and classified as "research without risk" due to medical records as data source.

Source

A consecutive sampling technique was applied. Study begun with a total population of 30 patients, who were the whole population who had undergone IPL at the Clinic and who fulfilled inclusion criteria: (meibomian gland dysfunction and symptomatic dry eye disease); 25 out of these 30 patients completed the three IPL sessions and had all the required data consigned on their medical records. Patients who did not attended the protocol according to the established times or who had a dry eye disease without evidence of glandular dysfunction or who undergone eye surgery a year before IPL treatment were excluded.

Follow up data

All patients had a complete ophthalmological exam including Non-Invasive Tear Break Up Time (tBUT) executed with a fluorescein strip, Schirmer's Test without anesthesia and ocular surface staining with Lissamine Green graded by the Van Bijsterveld Score (a 0–9 staining scale).[25] The severity of the symptoms was quantified on a visual analog scale ranging from 0 to 10, where 0 was symptom-free and 10 was the presence of permanent and incapacitating symptoms (referred as eye pain, ocular discomfort and foreign body sensation). All patients continued their previous dry eye medications and their eyelid massage after warm compresses, as they did before IPL therapy without any modification.

Based on the IPL indications, no analysis of systemic diseases was required.

Treatment protocol

The equipment used was the E-eye, IPL therapy machine (E-SWIN, Paris, France). Each patient was categorized according to his/her skin type according to Fitzpatrick,[26] and the treatment intensity (9.8–13.0 J/cm^2) assigned accordingly; so lighter skin types (Fitzpatrick I) received greater intensity treatments (13.0 J/cm^2) and darker skin types (Fitzpatrick IV) received lesser intensity treatments (9.8 J/cm^2); IPL therapy was deemed contraindicated for dark skin types (Fitzpatrick VI).

All patients kept their previous pharmacological management during the therapy timeframe, and the use at home of warm eyelid compresses and lid massage were kept as well. After that, each patient received three sessions (day 0, 15 and 45) that comprised warm eyelid compresses during 7 min, manual expression of Meibomian Glands, application of conducting gel over the zygomatic areas (E-eye laboratories), application of five flashes of xenon light in each zygomatic area starting below the inner canthus and extending out close to the tragus, and finally ending with a second manual expression of the Meibomian Glands An ophthalmological control was done 30 days after the last session, revising both symptoms and objective findings of dry eye.

No anti-inflammatory eye drops were used during IPL sessions or during 6 weeks treatment.

Statistical analysis

Instead of a sample size, the whole population who received the treatment was included. Microsoft Office Excel was used for data recollection, and SPSS 21.0 for iOS for the analysis. Categorical variables were presented as number and percentage, and values of continuous variables with median and interquartile range according to their non-normal distribution; they were calculated with the Kolmogorov–Smirnov test.

For the subgroup analysis, a case selection was made using such function on the SPSS program, employing the "satisfy the interest" requirement to compare the rosacea and Sjogren groups and excluding the other etiologies.

For the bi-variate analysis a chi-square test was employed for categorical variables, the Mann–Whitney *U* test was used for independent continuous variables and the Wilcoxon test for repeated measure variables analysis. For the significance an alpha level of 0.05 was set.

Results

Data from 50 eyes (25 patients) was recollected. There were 9 men (36%) and 16 women (64%), all of them with dry eye diagnosis, and with a punctual prevalence of Rosacea of 80% ($n = 20$) and Sjögren's of 16% ($n = 4$) of the total group; the remaining percentage (4%) was classified as evaporative dry eye disease secondary to Meibomian Gland Dysfunction.

Median age was 59 yrs. (IQR 52–64 yrs), and data from both eyes results was obtained from all patients.

The median of the subjective score (symptoms) before treatment was 8 (IQR 8–9) and upon finishing treatment was 3 (IQR 2–4) ($p < 0.05$).

Regarding objective dry eye disease evaluation at the beginning and end of treatment, a median tBUT of 4 (IQR 3–5) and 10 (IQR 8–11), a Schirmer of 13 (IQR 12–15) and 15 (IQR 13–20) and Van Bijsterveld score of 3 (IQR 3–4) and 2 (IQR 2–3) were respectively found ($p < 0.05$ on all analysis performed with Wilcoxon Test for repeated measurements).

Subgroup analysis for the Rosacea and Sjögren's diagnosis groups is presented in Table 1, were findings between groups were compared and the results before and after as well.

There were no complications or worsening during treatment.

Discussion

This study presents satisfactory results on 50 eyes (25 patients) with a diagnosis of dry eye after applying IPL; there was a clear improvement both on the subjective score as well as the objective tests done at the office, placing IPL as an excellent supplement for the management of dry eye patients who do not improve enough upon conventional treatment with eye

Table 1 – Subgroup analysis: Rosacea and Sjögren.

	Dry eye type				Statistic significance
	Rosacea ($n=40$)		Sjögren ($n=8$)		
	Median	IQR	Median	IQR	p Value*
Initial symptoms	8	8–9	8	7.25–9	0.83
Final symptoms	2	2–4.75	5.5	3–7.75	<0.05
p Value**	<0.05		<0.05		
Initial tBUT	4	3–4.75	4	3.25–5	0.21
Final tBUT	10	8–11	9	8–10	0.28
p Value**	<0.05		<0.05		
Initial Schirmer	13.5	12–15	7.5	3–11.75	<0.05
Final Schirmer	15	13–18	15.5	9.25–20.75	0.90
p Value**	<0.05		0.68		
Initial VB	3	3–4	4	2.75–4.25	0.61
Final VB	3	2–3	3	2–3	0.89
p Value**	<0.05		0.63		

The table shows a subgroup analysis, where the Rosacea and Sjögren patients were grouped and compared between them (horizontal) or compared themselves before and after the treatment (vertical).

* Contrast Hypothesis Test: Mann–Whitney's U (normality: Shapiro–Wilk).

** Contrast Hypothesis Test: Wilcoxon's (normality: Shapiro–Wilk).

Total n on this analysis: 48 eyes.

tBUT: Non Invasive Tear Break UpTime.

IRQ: interquartile range.

drops and punctum plugs. Improvement was observed both on the evaporative type as well as on the predominantly aqueous deficient one, suggesting that this last group of patients have an associated evaporative component frequently underestimated.

IPL therapy has been used in humans since 1996 for the management of undesired facial hair, vascular and pigmented skin lesions, and for neurogenic pain control, among others.[20,27,28] It is been used in ophthalmology since 2002 for dry eye disease adjuvant control, with consistent reports of subjective and objective improvement in both evaporative as aqueous deficient dry eye disease.[13,15-18,21,24,29]

It's mechanism of action in dermatology seems to be pretty well defined, its targets being the skin pigments, either melanin or blood, which absorb the light directly and transfer it to the nearby tissues.[21,22,24]

The mechanism of action in dry eye disease are less clear, and there is no consensus on it; among the proposed are abnormal blood vessels thrombosis, meibum heating and liquefaction, photomodulation, *Demodex* eradication, secretion modulation of pro and anti-inflammatory molecules, and Matrix Metalloproteinases (MMP's) suppression.[12,13,17,22,30]

However, this mechanisms do not explain satisfactorily the local therapeutic effect at the palpebral level (more specifically, on the Meibomian Glands), considering that vascular thrombosis and warming and liquefaction of the meibum do not take effect due to the distance from the zygomatic area (where treatment is applied) to the eyelid, and because the temperature increment is very subtle, short timed and confined to be able to warm those distant tissues. Likewise, *Demodex* eradication is hardly due to distant heat application; more likely it is a result of the adjunct local therapy offered to these patients and their increased willingness to follow it.

Finally, it is difficult to explain the secretion modulation of pro and anti-inflammatory molecules as a direct effect of local vascular alterations when the applied treatment is low intensity and distant; as a matter of the fact therapeutic results in Meibomian Gland Dysfunction are the same when IPL is applied directly on the eyelids as when it is conventionally applied on the zygomatic area, which suggests that the effect obtained does not depend on temperature rise or physical proximity of the treatment itself.[13]

Contrary to the above-mentioned action mechanisms, we think that the main mechanism of action of IPL on the eyelids is secondary to its effects on the tarsal plate mitochondria. Different from laser treatments, IPL therapy for Meibomian gland dysfunction is not an ablative nor thermal procedure, but has a photochemical effect equivalent to plants photosynthesis were light is absorbed and induces a chemical modification. The mechanism of action of this non-laser light at the cellular level is based on the absorption of monochromatic visible and near infra-red (NIR) spectrum light by the cellular respiratory chain components. Phototherapy is characterized by its capability to trigger photobiologic processes at the cellular level. Mitochondria play a crucial role on energy generation and cellular metabolism; the inner mitochondrial membrane has five integrated protein complexes, among which is the Cytochrome C Oxidase (Cco) Complex that has been proposed as the primary photo-receptor of the near infrared range light on mammal cells.[23,31]

It is on those mitochondria were light exerts its initial effect, yielding an increase on ATP production, reactive oxygen modulation and the induction of transcription factors. Altogether, these effects produce a proliferation and cellular migration increment at the acini on the Meibomian Glands, as well as modulation in cytokines, growth

factors, and inflammatory mediator levels, and finally an increase in cellular oxygenation,[28] all of which helps to explain the multiple local palpebral therapeutic effects of IPL.

In this study we noted a statistically significant improvement in signs and symptoms of patients with not only evaporative dry eye disease secondary to Rosacea, but also on Sjögren's aqueous deficient ones. Results on Rosacea patients are to be expected due to the IPL mechanism of action. However, the subjective and objective improvement on Sjögren Syndrome patients should not be a surprise as it is well known that many of those patients have an evaporative component frequently under-estimated; subjective improvement in this group is not as strong as the objective improvement, but it is well known that in Sjögren Syndrome patients there is a wide discordance between signs and symptoms.

IPL therapy is an effective and reproducible adjuvant method for the management of evaporative and/or mixed dry eye.

This treatment has been received by the ophthalmological community with skepticism mainly because its mechanism of action has not been clearly elucidated. We think its main mechanism of action lies in the mitochondrial activation, which explains its effectivity at the palpebral level when applied at distance on the zygomatic area.

Conflict of interest statement

The authors declare they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial interest in the subject matter or materials discussed in this manuscript.

REFERENCES

1. Craig JP, Nichols KK, Akpek EK, Caffery B, Dua HS, Joo CK, et al. TFOS DEWS II Definition and classification report. Ocul Surf. 2017;15:276–83.
2. Stapleton F, Alves M, Bunya VY, Jalbert I, Lekhanont K, Malet F, et al. TFOS DEWS II epidemiology report. Ocul Surf. 2017;15:334–65.
3. Pflugfelder SC, Solomon A, Stern ME. The diagnosis and management of dry eye: a twenty-five-year review. Cornea. 2000;19:644–9.
4. Rabensteiner DF, Aminfar H, Boldin I, Schwantzer G, Horwath-Winter J. The prevalence of Meibomian gland dysfunction, tear film and ocular surface parameters in an Austrian dry eye clinic population. Acta Ophthalmol. 2018;96:E707–10.
5. Jones L, Downie LE, Korb D, Benitez-del-Castillo JM, Dana R, Deng SX, et al. TFOS DEWS II Management and therapy report. Ocul Surf. 2017;15:575–628.
6. Korb DR, Blackie CA, Finnemore VM, Douglass T. Effect of using a combination of lid wipes, eye drops, and omega-3 supplements on Meibomian gland functionality in patients with lipid deficient/evaporative dry eye. Cornea. 2015;34:407–12.
7. Epitropoulos AT, Donnenfeld ED, Shah ZA, Holland EJ, Gross M, Faulkner WJ, et al. Effect of oral re-esterified omega-3 nutritional supplementation on dry eyes. Cornea. 2016;35:1185–91.
8. Foulks GN, Borchman D, Yappert M, Kakar S. Topical azithromycin and oral doxycycline therapy of Meibomian gland dysfunction: a comparative clinical and spectroscopic pilot study. Cornea. 2013;32:44–53.
9. Kashkouli MB, Fazel AJ, Kiavash V, Nojomi M, Ghiasian L. Oral azithromycin versus doxycycline in Meibomian gland dysfunction: a randomised double-masked openlabel clinical trial. Br J Ophthalmol. 2015;99:199–204.
10. Dougherty JM, McCulley JP, Silvany RE, Meyer DR. The role of tetracycline in chronic blepharitis. Inhibition of lipase production in staphylococci. Invest Ophthalmol Vis Sci. 1991;32:2970–5.
11. Shafaa MW, el Shazly LH, el Shazly AH, el gohary AA, el hossary GG. Efficacy of topically applied liposome-bound tetracycline in the treatment of dry eye model. Vet Ophthalmol. 2011;14:18–25.
12. Jiang X, Lv H, Song H, Zhang M, Liu Y, Hu X, et al. Evaluation of the safety and effectiveness of intense pulsed light in the treatment of Meibomian gland dysfunction. J Ophthalmol. 2016;2016, 1910694.
13. Rong B, Tang Y, Tu P, Liu R, Qiao J, Song W, et al. Intense pulsed light applied directly on eyelids combined with Meibomian gland expression to treat Meibomian gland dysfunction. Photomed Laser Surg. 2018;36:326–32.
14. Dell SJ. Intense pulsed light for evaporative dry eye disease. Clin Ophthalmol Auckl N Z. 2017;11:1167–211673.
15. Vora GK, Gupta PK. Intense pulsed light therapy for the treatment of evaporative dry eye disease. Curr Opin Ophthalmol. 2015;26:314–8.
16. Toyos R, McGill W, Briscoe D. Intense pulsed light treatment for dry eye disease due to Meibomian gland dysfunction: a 3-year retrospective study. Photomed Laser Surg. 2015;33:41–6.
17. Gupta PK, Vora GK, Matossian C, Kim M, Stinnett S. Outcomes of intense pulsed light therapy for treatment of evaporative dry eye disease. Can J Ophthalmol. 2016;51:249–53.
18. Dell SJ, Gaster RN, Barbarino SC, Cunningham DN. Prospective evaluation of intense pulsed light and Meibomian gland expression efficacy on relieving signs and symptoms of dry eye disease due to Meibomian gland dysfunction. Clin Ophthalmol Auckl N Z. 2017;11:817–27.
19. Craig JP, Chen Y-H, Turnbull PRK. Prospective trial of intense pulsed light for the treatment of Meibomian gland dysfunction. Invest Ophthalmol Vis Sci. 2015;56:1965–70.
20. American Medical Bio Care Inc. – Newport Beach, California Corporate Background webarchive.
21. Wat H, Wu DC, Rao J, Goldman MP. Application of intense pulsed light in the treatment of dermatologic disease: a systematic review. Dermatol Surg. 2014;40:359–77.
22. Huang Y-Y, Sharma SK, Carroll J, Hamblin MR. Biphasic dose response in low level light therapy an update. Dose Response. 2011;9:602–18.
23. Babilas P, Schreml S, Szeimies R-M, Landthaler M. Intense pulsed light (IPL): a review. Lasers Surg Med. 2010;42:93–104.
24. Li D, Lin S-B, Cheng B. Intense pulsed light: from the past to the future. Photomed Laser Surg. 2016;34:435–47.
25. Karu T. Laser biostimulation: a photobiological phenomenon. J Photochem Photobiol B. 1989;3:638–40.
26. Godin MR, Stinnett SS, Gupta PK. Outcomes of thermal pulsation treatment for dry eye syndrome in patients with Sjögren disease. Cornea. 2018;37:1155–8.

27. Van Bijsterveld OP. Diagnostic tests in the Sicca syndrome. Arch Ophthalmol. 1969;82:10–4.
28. Roberts WE. Skin type classification systems old and new. Dermatol Clin. 2009;27:529–33.
29. IEEE J Sel Top Quantum Electron. 2016;22:77000417.
30. Liu R, Rong B, Tu P, Tang Y, Song W, Toyos R, et al. Analysis of cytokine levels in tears and clinical correlations after intense pulsed light treating Meibomian gland dysfunction. Am J Ophthalmol. 2017;183:81–90.
31. Karu TI, Afanas'eva NI. Cytochrome C oxidase as the primary photoacceptor upon laser exposure of cultured cells to visible and near IR-range light. Dokl Akad Nauk. 1995;342:693–5.