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Blue diode laser as supportive therapy for the management of vulvar lichen sclerosus

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Ethical approval: For each patient written informed consent was acquired. The study was conducted according to the Declaration of Helsinki declaration of 1975 as revised in 2013 and in accordance with the ethical standards of the responsible committee on human experimentation.

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Abstract
Vulvar lichen sclerosus is a chronic inflammatory condition characterized by the thinning and atrophy of the skin and mucosa surrounding the vulva and anus. This study evaluates the efficacy of a treatment protocol utilizing blue-diode laser photobiomodulation in managing vulval lichen sclerosus symptoms in a cohort of 12 female patients. The treatment protocol consisted of laser sessions for 3 times a week for 2 weeks, and follow-up sessions over a 16-week period. Objective and subjective parameters were assessed before treatment, at the end of treatment, and at 4-month follow-up visits. Results demonstrated significant reductions in subjective symptoms such as itching and pain, as well as improvements in objective signs including erythema and fissures. No side effects were observed, indicating the safety and tolerability of laser treatment. These findings suggest that photobiomodulation can be an effective therapeutic option for patients with vulval lichen sclerosus, with future research aimed at refining treatment protocols and evaluating its long-term benefits.

Introduction

Lichen sclerosus (LS) is a chronic Th1-mediated inflammatory condition affecting females at a ratio of 3:1 compared to males. Exhibiting a predilection for genital areas in both sexes, the condition manifests through the atrophy and thinning of the skin and mucosa surrounding the vulva and anus, displaying a chronic course marked by recurring episodes that eventually result in vulval atrophy, adhesions, formation of scars, and disruption of normal vulval anatomy and function[1]. Typical features include depigmented spots, either hyperkeratotic or sclerotic, that may be surrounded by erythema and accompanied by fissures, purpura and ecchymoses. The Koebner phenomenon, wherein lesions develop in previously unaffected skin following scratching or other forms of trauma, is a well-recognized characteristic of this disease. LS is characterized histologically by hyperkeratosis, dermal atrophy, basal cell degeneration, dermal hyalinization, and a band-like lymphocytic infiltrate[1]. Onset can occur at any age, with incidence peaking twice - once in adolescence and again in post-menopausal years.

Patients with LS face an increased risk of developing genital squamous cell carcinoma, necessitating long-term follow-up[2]. Despite being of unknown etiology, evidence suggests an autoimmune basis, with a reported family history in 12% of cases[1,3].

Topical steroids, particularly super-potent ones like 0.05% clobetasol propionate cream or ointment, constitute the cornerstone of treatment. Additional therapeutic options include topical calcineurin inhibitors, topical sex hormones, topical and systemic retinoids, emollients, anti-TNF alpha biological agents, UVA-1 phototherapy, ablative and non-ablative laser therapies[4-8].

Beyond its physical manifestations, LS significantly impacts the quality of life, particularly in the realms of psycho-sexual well-being[1,3,9].

This study aims to evaluate the efficacy of a treatment protocol with blue-diode laser photobiomodulation (PBM) in female patients diagnosed with LS.

Materials and Methods

The present single-center, single-blind prospective study was conducted from May 2022 to May 2023 at the Unit of Oral and Maxillo Facial Surgery (Ca' Foncello Hospital, Treviso) in collaboration with the Dermatology Unit at Ca' Foncello Hospital, Treviso, Italy.

The main objective of the study was to evaluate the efficacy of PBM performed with a blue-diode laser in the management of vulval lichen sclerosus (VLS) in terms of 50% reductions of signs and symptoms over time.

Study protocol

The present study protocol was born following the consolidated collaboration between the Unit of Oral and Maxillofacial Surgery and the Dermatology Unit of the Ca' Foncello Hospital, especially for the management of mucocutaneous diseases like lichen planus.

In our setting, patients with oral lichen planus are screened for extraoral cutaneous lesions by dermatologists and patients with genital involvement are evaluated by dentists and maxillofacial surgeons for oral features of the disease.
The use of Blue Diode Laser is already documented as an effective technique for multiple conditions[10-13], including the management of LS[14]. Nonetheless, literature still lacks robust evidence and protocols are not standardized yet.
Twelve consecutive female patients affected by histologically confirmed VLS without oral involvement and not entirely satisfied with the ongoing treatment, were recruited for the treatment with blue diode laser. Inclusion criteria were: histological and clinical diagnosis of genital LS, female sex, age higher than 18 years, availability to attend scheduled appointments. The only allowed treatments during the study protocol were emollients. Topical steroids and topical calcineurin inhibitors had to be discontinued for at least 2 weeks; systemic therapies (acitretin/dapsone) could be continued during the study.
Exclusion criteria were: male sex, age lower than 18 years, pregnancy or lactation, extragenital localization of lichen sclerosus, previous diagnosis of ano-genital neoplasia, previous genital radiotherapy or laser therapy, acute or chronic infections such as syphilis, vulvo-vaginitis or HIV, application of pigmented topical products (eg eosine, jodopovidone), concurrent treatment with topical steroids or topical calcineurin inhibitors. All the patients signed an informed consent before proceeding to the treatment.
Patients were subjected to PBM therapy three times a week for two weeks and were then evaluated in follow-up sessions. The following protocol was employed and repeated two consecutive times during each daily session in defocused modality: combined wavelengths 445+/-15, 970+/-15 and 660+/-15 nm, frequency 50-1000 Hz, peak power 6 W, 240 s, spot size 2 cm^2, and 600 J energy (GaAIAs diode laser, Eltevh K-Laser Srl, Treviso, Italy). The fiber was kept orthogonally and moved with concentric circles all over the affected area and kept about 3-cm distance from the lesions. Both patients and operators wore goggles during the laser therapy sessions.
One dermatologist (SB) performed the laser sessions and other colleagues (AG, SC), who were blinded as regards as the treatment applied, performed the clinical evaluation of outcomes.
For each patient a series of subjective and objective parameters were evaluated before starting the treatment (T0), at the end of the treatment (T2) and 4 months after the end of therapy (T16).
We used a modified Clinical Lichen Sclerosus Score[4] assessing the following items: itch, pain, dysuria with a 11-point scale from 0 (absent) to 10 (the worst condition ever); erythema, whitening, petechiae, fissures, clitoral hood fusion, labial fusion, anterior changes, perianal involvement, formation of posterior commissure band with a 4-point score (0: absent, 1: mild, 2: moderate, 3: severe). For each patient, DLQI (Dermatology Life Quality Index) [15] score was assessed at T0, T2 and T16. Digital photographs were taken at each visit.

Statistical analysis
Python version 3.9.16, Scipy 1.7.3, Pandas 1.4.4 were used for data analysis. Friedman test with Bonferroni corrections was used to evaluate changes over time. The achievement of the main goal of the study, namely the 50% reduction in signs and symptoms of VLS, was assessed using the Cochrane Q test by comparing T0 with T2 and T16 (start and end of laser treatment, start and follow-up visit at 4 months) and T2 with T16 (end of laser treatment and follow-up visit at 4 months).

Results
Twelve consecutive female patients were enrolled in the present study. Demographic features, comorbidities, duration of VLS and previous therapies are shown in Table 1.
The mean age was 57,4 years (± 12,1 years), 25% of patients reported a disease duration of less than 5 years, 41,7% between 5 and 10 years, 33,3% more than 10 years. Most patients reported at least one comorbidity (7 out of 12, 58,3%), among which the most frequent was arterial hypertension (33,3%). Three patients (25%) reported autoimmune concomitant conditions such as Hashimoto

thyroiditis and localized scleroderma. All the patients were previously treated with clobetasole propionate 0.05% ointment, that was stopped at least 14 days before PBM and discontinued until T16. Table 2 and table 3 show results of every parameter considered, analysed with Friedman test with Bonferroni corrections and with Cochran Q test, respectively.
Subjective symptoms reported by patients such as itch and pain significantly decreased over time ($p=0.0071$ and $p=0.0001$ respectively), both parameters reached the attended 50% improvement at T2 and T16. DLQI showed significant reduction over time ($p=0.0004$), DLQI values improved of at least 50% comparing T0 and T2 and T0 and T16 with statistical significance ($p=0.0027$ and $p=0.0143$, respectively). No statistically significant data were found between T2 and T16 meaning that the improvement was maintained after the end of laser sessions up to T16 (Table 2 and Table 3).
Objective signs such as anterior changes, erythema, fissures, perianal involvement and whitening significantly improved over time, each parameter significantly reached the 50% improvement after PBM and T16. More chronic signs such as clitoral and labial fusion and the presence of petechiae did not change over time and did not significantly improve after PBM (Table 2, Table 3, Figure 1). The evaluation of objective signs was performed through photographic comparison.
All patients completed PBM and attended to follow up. No side effects were detected and no patients discontinued the treatment.

Discussion

The present paper deals with the efficacy of PBM in the management of VLS in a cohort of 12 patients.
The employment of PBM in the management of symptoms in various inflammatory conditions is widespread[16,17], as it is for gynecological pathologies[18]. Treatment of VLS focuses on inflammation reduction and minimization of the sequelae.
In most studies, PBM in compared with topical steroids- as the goal standard of treatment- and laser therapy is frequently associated with greater reduction in itching, pain, and dyspareunia at around 1 and 3 months after treatment. Also, subjective outcomes, tolerability and patients 'satisfaction show better results for PBM than topical steroids[19].
Lasers are emerging strategies for treating VLS. Antinflammatory and biostimulating properties are the main rationales for their increased use, also at the histopathological level. In fact, lasers act at the collagen and epithelial level, avoiding the progressive (or maintained) thinning induced by prolonged steroid therapy[20]. Some authors also demonstrated that sclerosis can be greatly reduced after PBM[21].
The efficacy of PBM depends on treatment parameters and despite it is usually well-tolerated and free of side effects, the expected therapeutic effect can be achieved only with the correct parameters. Endogenous cromophores adsorb red and near infrared lights and modulate mitochondrial adenosine triphosphate, generate reactive oxygen species and modify intracellular calcium levels, promoting cell proliferation, migration and differentiation. All these mechanisms contribute to wound healing, analgesia and tissue regeneration[22].
The combination of wavelengths applied in our treatment protocol is quite a unique feature, since it offers multiple advantages in terms of biostimulation, heat control, analgesia and antimicrobial effects. The choice of the correct protocol represents a milestone in current research in PBM and the use of specific protocols depending on the expected effect prompts the validation of a multiwavelength protocol in the clinical settings[12].
Many reports confirm that combining red and blue light accelerates re-epithelization and cross-linked collagen fibers formation[23], while it is hypothesized that infrared wavelengths may contribute to the reduction of hypertrophic wound healing[24]. Moreover, lasers impact on pain transmission, modulating nociception having mitochondria as the primary target, reducing adenosine triphosphate content and increasing reactive oxygen species levels. The 970nm infrared wavelength seems to act also on the reduction of calcium response, configurating as the ideal wavelength for analgesia[25].
To the best of our knowledge, only one study experimented the use of blue diode laser in VLS[14], whereas a few discussed other types of devices like CO_2[26] - the most studied- Nd:YAG[5] and

Er:YAG[27] . Despite this, the blue light appears to shape up for the purpose of healing VLS since it enhances the healing process in chronic and hard-to-heal wounds that do not respond to standard treatment, thanks to promotion of angiogenesis, reduced inflammation, and direct antimicrobial effects[28,29].

The present study demonstrates rapid benefit on both subjective symptoms (itching, pain, quality of life) and objective signs (erythema, fissures, anterior changes, perianal involvement, whitening), with the benefit sustained over time (16 weeks). No side effects were observed, indicating that the treatment is safe and well-tolerated.

Future objectives include evaluating a larger sample size, conducting multicenter studies, and assessing the timing for retreatment.

The rapid and sustained efficacy of the treatment observed in this study underscores its potential as a valuable therapeutic option for patients suffering from the condition. Further research and collaboration are needed to fully elucidate its long-term benefits and optimal use in clinical practice.

Conclusions

In conclusion, this study highlights the efficacy of PBM in managing symptoms associated with VLS in a cohort of 12 patients. The findings reveal rapid and sustained improvement in both subjective symptoms and objective signs over a 16-week period, with no observed side effects, indicating the safety and tolerability of the treatment. Moving forward, future objectives include expanding the sample size, conducting multicenter studies, and optimizing retreatment strategies. The results of this study underscore the potential of PBM as a valuable therapeutic option for VLS patients. However, further research and collaboration are warranted to fully understand its long-term benefits and refine its clinical application.

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Table 1. Demographic data, disease duration, previous treatments and comorbidities of patients enrolled in the study.

	Age (years)	Duration of LS	Previous therapies and outcomes	Comorbidities
Patient 1	80	> 10 years	Clobetasole ointment: mild improvement	arterial hypertension, glaucoma
Patient 2	53	> 10 years	Clobetasole ointment: ineffective, acitretin: mild improvement	Hereditary palmo-plantar cheratoderma
Patient 3	55	> 10 years	Clobetasole ointment: ineffective, dapsone tablets: ineffective	Localized scleroderma of the trunk
Patient 4	70	> 10 years	Clobetasole ointment: mild improvement, tacrolimus ointment: suspended for side effects (irritation)	arterial hypertension, autoimmune hypothiroidism, type 2 diabetes
Patient 5	58	between 5 and 10 years	Clobetasole ointment suspended for side effects (irritation), dapsone tablets suspended for lack of efficacy	arterial hypertension
Patient 6	58	between 5 and 10 years	Clobetasole ointment: mild improvement	arterial hypertension
Patient 7	51	< 5 years	Clobetasole ointment suspended for lack of efficacy, tacrolimus ointment: mild improvement	none
Patient 8	58	between 5 and 10 years	Clobetasole ointment: mild improvement	autoimmune hypothiroidism
Patient 9	58	between 5 and 10 years	Clobetasole ointment: suspended for lack of efficacy	none
Patient 10	28	< 5 years	Clobetasole ointment: mild improvement	none
Patient 11	62	between 5 and 10 years	Clobetasole ointment: mild improvement	none
Patient 12	58	< 5 years	Clobetasole ointment: mild improvement	none

Table 2. Evaluation of any parameter over time (T0, T2, T16) with Friedman T test with Bonferroni correction.

Symptom / Sign	Time	Mean	Std	Friedman Test p (with Bonferroni Correction)
Dysuria	T0	1.33	2.23	0.0740
	T2	0.17	0.58	
	T16	0.25	0.62	
Itch	T0	5.33	3.92	0.0071*
	T2	1.58	2.57	
	T16	1.50	1.78	
Pain	T0	3.92	2.35	0.0001*
	T2	0.75	1.86	
	T16	1.08	2.11	
DLQI	T0	9.08	4.70	0.0004*
	T2	3.92	3.03	
	T16	5.33	4.83	
Anterior Changes	T0	1.58	0.79	0.0024*
	T2	0.92	0.79	
	T16	0.92	0.51	
Clitoral Fusion	T0	0.67	0.98	n.s.
	T2	0.67	0.98	
	T16	0.67	0.98	
Erythema	T0	2.42	0.51	0.0000*
	T2	0.00	0.00	
	T16	0.50	0.80	
Fissures	T0	1.00	0.85	0.0024*
	T2	0.08	0.29	
	T16	0.33	0.49	
Labial Fusion	T0	1.17	1.03	0.2231
	T2	1.08	1.00	
	T16	1.00	1.04	
Perianal Involvement	T0	1.33	0.98	0.0006*
	T2	0.42	0.67	
	T16	0.67	0.78	
Petechiae	T0	0.17	0.39	0.1353
	T2	0.00	0.00	
	T16	0.00	0.00	
Posterior Commissure Bands	T0	0.58	0.79	0.1653
	T2	0.33	0.65	
	T16	0.33	0.65	
Whitening	T0	2.25	0.75	0.0001*
	T2	0.83	0.39	
	T16	0.75	0.45	

STD: standard deviation, n.s.: not significant, *statistically significant (p=0.025)
T0: before starting laser therapy, T2: after two weeks (at the end of laser therapy sessions), T16: after 16 weeks

Table 3. Cochran Q test was used to assess the improvement of 50% of each parameter comparing T0 and T2, T0 and T16, T2 and T16.

Symptom / Sign	**Time**	**Cochran Q Test p (50% improving)**
Dysuria	T0-T2	0.0455*
	T0-T16	0.0455*
	T2-T16	n.s.
Itch	T0-T2	0.0082*
	T0-T16	0.0047*
	T2-T16	0.0455*
Pain	T0-T2	0.0027*
	T0-T16	0.0027*
	T2-T16	n.s.
DLQI	T0-T2	0.0027*
	T0-T16	0.0143*
	T2-T16	0.0833
Anterior Changes	T0-T2	0.0047*
	T0-T16	0.0143*
	T2-T16	0.3173
Clitoral Fusion	T0-T2	n.s.
	T0-T16	n.s.
	T2-T16	n.s.
Erythema	T0-T2	0.0005*
	T0-T16	0.001*
	T2-T16	n.s.
Fissures	T0-T2	0.0082*
	T0-T16	0.0143*
	T2-T16	n.s.
Labial Fusion	T0-T2	0.3173
	T0-T16	0.1573
	T2-T16	0.3173
Perianal Involvement	T0-T2	0.0047*
	T0-T16	0.0253*
	T2-T16	n.s.
Petechiae	T0-T2	0.1573
	T0-T16	0.1573
	T2-T16	n.s.
Posterior Commissure Bands	T0-T2	0.0455*
	T0-T16	0.0455*
	T2-T16	n.s.
Whitening	T0-T2	0.0009*
	T0-T16	0.0016*
	T2-T16	0.1573

T0: before starting laser therapy, T2: after two weeks (at the end of laser therapy sessions), T16: after 16 weeks
n.s.: not significant, *statistically significant ($p<0.05$)

Figure 1. Clinical pictures of a patient over time: a. T0 before starting the treatment severe erythema, fissures, whitening, clitoral and labial fusion are present; b. T2 after PBM fissures and erythema are diminished; c. T16 four months after PBM good clinical outcome with mild fissures and whitening.