CEOG Clinical and Experimental Obstetrics & Gynecology

Carbon dioxide laser as a new valid treatment of lichen sclerosus

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Summary

Purpose of Investigation: To investigate the role of CO_2 laser in the patients affected by lichen sclerosus (LS), analyzing histological changes and relief of feminine discomfort. *Materials and Methods:* The authors report a case series of ten patients with histologically verified LS, undergoing fractional CO_2 laser, from January 2017 to December 2017. The mean age of the participants was 55 (range 40–68) years, and five had been previously treated with the topical corticosteroid clobetasol propionate 0.05% ointment with limited efficacy. The overall sessions varied depending on the lichen extension, from one to three treatments. *Results:* All the patients tolerated the procedure well with re-epithelialization occurring within 3–4 weeks in all cases. Carbon dioxide laser was successful in achieving remarkable symptoms reduction or remission. There was an improvement in the appearance of the introitus, and in elastic opening and closing. Post-treatment histology revealed trophic epithelium with mild acanthosis and small areas with superficial hyperkeratosis. These results were maintained throughout the three-month post-treatment follow-up period. *Conclusion:* Laser treatment is relatively simple and effective. The histological changes observed in these patients suggest a more comprehensive healing effect of the fractional CO_2 laser, not only symptomatic approach. The authors await the next follow-up to establish the duration of the effects. *Content:* CO_2 laser is a valid treatment option for LS, improving discomfort through histological changes of tissue.

Key words: Laser CO_2; Lichen sclerosus; Itch; Dyspareunia; Vulva.

Introduction

Lichen sclerosus (LS) is a chronic, inflammatory skin condition, most commonly occurring in adult women, although it can also be seen in men and children, with a reported female-to-male ratio from 10:1 to 5:1 [1-3]. It primarily affects the genital and perianal regions, but it can also involve extragenital regions [4]. The exact etiology and pathogenesis are unknown and there is increasing evidence of autoimmune mechanisms as a role. A genetic susceptibility to LS is assumed: chronic irritation of the genital epithelium may lead to previously sequestered site-specific skin epitopes being revealed and that those patients with an autoimmune diathesis would subsequently be more likely to develop autoantibodies [5]. Oyama *et al.* [6] showed in 2003 that in 75% of all patients with LS, auto-antibodies to extracellular matrix protein 1 could be detected [3].

A minority of patients with vulvar LS (VLS) are asymptomatic but most report significant itch, (especially in the evening as a key symptom), discomfort, dyspareunia, burning pain, and dysuria. LS left untreated has significant potential to result in the destruction of the vulval architecture: stenosis of introitus vaginae and labial fusion can occur [3]. Spontaneous remission is extremely rare and affected people have an increased risk of squamous cell carcinoma (SCC) of the vulva [3, 7].

The diagnosis of LS is usually clinical. Biopsy to rule out SCC is recommended in all patients suspected of having LS, when malignancy cannot be excluded or in those who have failed to respond to first line treatment. Therapeutic agents for LS include topical corticosteroids, which require continuous administration and patient adherence. Surgical approaches include vulvectomy and cryosurgery; however, these procedures leave scars on the damaged tissues and are associated with high recurrence rates [7].

Superficial ablation of LS by means of a CO_2 laser has been known for a long time [7, 8]. While considered a standard inpatient procedure, the technique requires use of general anesthesia and a healing period of six weeks.

Advancements in fractionated laser technology, which do not entail use of general anesthesia and incur minimal superficial ablation, alongside thermal cell activation and tissue rejuvenation, have raised the popularity of this treatment approach [8] also in the vulvo-vaginal area. The histological changes, manifested by thickening of vaginal epithelium enriched with collagen and neovascularization in the lamina propria [9].

This novel therapeutic fractionated CO_2 laser treatment option has been introduced as an efficient mean of reversing the typical post-menopausal vaginal wall histology to the premenopausal architecture, via a probe designed specifically. The microablative action of the fractionated CO_2 laser stimulates the interaction of heat shock proteins 43, 47, and 70 [6], which brings to a localized increase in specific cytokines, which, in turn, activate fibroblasts to produce other components of the extracellular matrix, such

Revised manuscript accepted for publication October 3, 2018

Clin. Exp. Obstet. Gynecol. - ISSN: 0390-6663
XLVI, n. 2, 2019
doi: 10.12891/ceog4893.2019

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Table 1. — *Characteristics of patients 1-5.*

Characteristics	Case1 S.G.	Case 2 M.M.	Case 3 S.A.	Case 4 D.A.	Case 5 F.M.
Age	53	61	61	54	40
Menopause	Yes	Yes	Yes	Yes	No
Previous treatment	Clobesol	No	No	Clobesol, advatan	Clobesol
Distribution	Labia minora, left interlabial sulcus, perineum	Introitus, left labia minora	Bilateral labia majora and minora, intoitus	Clitoral areas interlabial sulcus, labia minora, introitus	Clitoral areas, introitus
Symptoms	Pruritus, Burning Dyspareunia	Pruritus, burning, dyspareunia, very mild dysuria	Pruritus, mild burning, dyspareunia	Pruritus, dyspareunia, mild burning	Pruritus, dyspareunia, mild burning, very mild dysuria
N. of CO_2 laser treatments	2	3	2	2	1
Symptoms resolution	Pruritus occasionally	Pruritus occasionally, mild dyspareunia, very mild burning	Very mild dyspareunia, occasional burning	Very mild dyspareunia	Very mild dyspareunia

Table 2. — *Characteristics of patients 6-10.*

Characteristics	Case 6 R. S	Case 7 I.F.	Case 8 S.E.	Case 9 M.S.	Case 10 P. E.
Age	48	52	64	65	53
Menopause	No	Yes	Yes	Yes	No
Previous treatment	Clobesol	No	No	No	Clobesol
Distribution	Perianal skin, introitus, clitoral areas, interlabial sulcus, left labia minora	Perianal skin, introitus, clitoral areas, interlabial sulcus, labia minora and majora	Labia minora, clitoral areas, introitus	Introitus	Labia majora
Symptoms	Pruritus, very mild burning	Pruritus, mild dyspareunia, mild burning, mild dysuria	Pruritus, dyspareunia, mild burning	Pruritus, very mild dyspareunia, burning, mild dysuria	Pruritus, very mild dyspareunia, and burning
N. of CO_2 laser treatments	2	3	2	1	2
Symptoms' resolution	Complete	Pruritus and burning, occasional mild dysuria	Pruritus, occasional dyspareunia	Very mild pruritus and burning, occasional dyspareunia	Occasional dyspareunia

Table 3. — *Results of laser therapy in patients with symptoms' persistence.*

Symptoms	Before treatment		After treatment	
	Number	%	Number	%
Pruritus	10	100	5	50
Dyspareunia	9	90	7	77
Burning	10	100	4	40
Urinary problems	4	40	1	25

Table 4. — *VAS scores.*

VAS symptoms	Before treatment		After treatment		*p* value
	Media	DS	Media	DS	
Pruritus	8.5	2.22	1.2	1.47	< 0.0001
Dyspareunia	6	3.13	2.3	2.41	0.0025
Burning	5.7	2.21	0.8	1.32	< 0.0001
Urinary problems	1.6	2.32	0.3	0.95	0.07 N.S.

as proteoglycans and glycosaminoglycans [10], hence new collagen and new blood vessels [8]. A fundamental role is played by transforming growth factor-beta (TGF-β), which stimulates the production of collagen, by fibroblast and epidermal growth factor (FGF and EGF) and stimulate neovascularization [11] and angiogenic activity, by platelet-derived growth factor (PDGF) vascular endothelial growth factor (VEGF), which promotes migration and proliferation of endothelial cells.

Overall, the resulting light-induced eutrophication process involves early thermal damage (within 48-72 hours of treatment), which is followed by a proliferation phase, with fibroblast recruitment and production of collagen and extracellular matrix (in the subsequent 30 days). Lastly, the remodelling phase (after 40 days) involves the apposition of mature collagen fibres and new elastic fibres [12].

The authors report a case series of ten patients undergo-

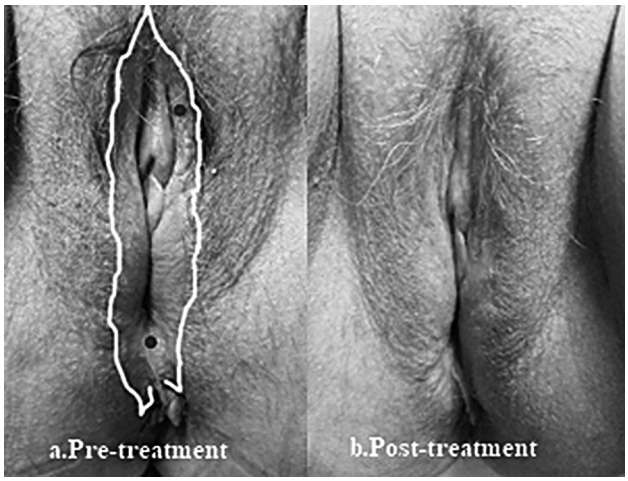

Figure 1. — Case 3: (a) pre-treatment and (b) post-treatment.

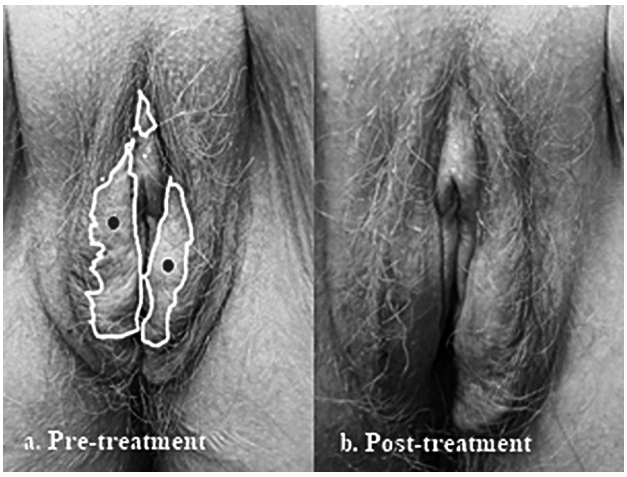

Figure 2. — Case 8: (a) pre-treatment and (b) post-treatment.

ing fractional CO_2 laser resurfacing for VLS.

Materials and Methods

Ten women with hyperkeratotic VLS were recruited from Gynecological Department of Cannizzaro Hospital from January 2017 to December 2017. All had biopsy-confirmed VLS. Five patients had been previously treated with the topical corticosteroid clobetasol propionate 0.05% ointment with limited efficacy, evidenced by ongoing symptoms, and lack of an objective response to treatment. None had a history of vulval intraepithelial neoplasia or SCC of the vulva. The mean age of the participants was 55 (range 40–68) years. Three patients were pre- menopausal and seven were post-menopausal. None had topic or systemic hormone replacement therapy (HRT). Pre-treatment assessments included a physical examination, assessment of global wellness, quality of life, and symptoms. The ten patients were symptomatic before treatment: especially intractable pruritus (in the evening as a key symptom) burning pain, atrophy, dyspareunia, and dysuria. These symptoms are often ignored by the patients or interpreted as secondary effects of Candida infection, vulvo-vaginitis, cystitis or non-specific irritations.

The clinical distribution of the LS varied (the interlabial sulcus, the labia minora and majora, perineum, and perianal skin) (Figures 1 and 2) and it is summarized in Tables 1 e 2, along with other relevant patient characteristics.

Once the need for treatment was confirmed, patients underwent CO_2 laser treatment sessions, performed at one-month intervals. Affected area was treated with one pass or two passes applied focally to more hypertrophic areas. The overall sessions varied depending on the lichen extension, from one to three treatments. The CO_2 laser was focused through holographic lenses to deliver microablative CO_2 laser energy via a specific probe. A topical anesthetic was applied to the lesion sites one hour prior to the procedure. The laser was set at low (10-15 Watts) 20-32 Mjoules by Pixel, or medium (30 Watts) 10 Mjoules by Pixel energy. Prophylactic topic antibiotics were given to the patients (azithromycin) for three days post-treatment. All patients tolerated the procedure very well.

Results

The patient suffered from pruritus (100%), sexual problems (90%), burning (100%), and also urinary problems (40%). Before the laser treatment 50% of the patients had previously received corticosteroid topical treatment without significant improvement of symptoms. These patients did not report any significant discomfort or other side-effects such as infection or bleeding. Re-epithelialization occurred within 3–4 weeks in all cases.

At the first follow-up examination, performed three months after the last treatment session, symptoms were evaluated using validated quality of life questionnaires. More specifically, the intensity was evaluated using a pain visual analogue scale (VAS) (0: complete absence of symptoms, 10: worst symptoms). All patients referred a clear improvement in their clinical signs and symptoms (Table 3). Pruritus disappeared in the 50% of the patient and reduced remarkable in the other 50%, with a media VAS from 8.5 ± 2.22 to 1.2 ± 1.47 ($p < 0.001$). Burning had a similar trend with a complete resolution in the 60% of the patients and a reduction in the VAS score (5.7 ± 2.21 to 0.8 ± 1.32). ($p < 0.001$). VAS score for all the symptoms before and after the treatment are summarized in Table 4.

Two of the nine women suffered from dyspareunia had complete resolution. The other seven had a great improvement with a media VAS 6 ± 3.13 at the beginning to 2.3 ± 2.41 ($p = 0.0025$). Conversely there was little improvement in the urinary problems. The four patients complaining of mild dysuria did not reach a significant improvement (VAS score 1.6 ± 2.32 to 0.3 ± 0.95) ($p = 0.07$, N.S.). There was an improvement in the appearance of the introitus and in elastic opening and closing.

As part of this visit, a biopsy vaginal mucosa sample was collected. Post-treatment histology revealed trophic epithelium with mild acanthosis and small areas with superficial hyperkeratosis (Figures, 3, 4, and 5).

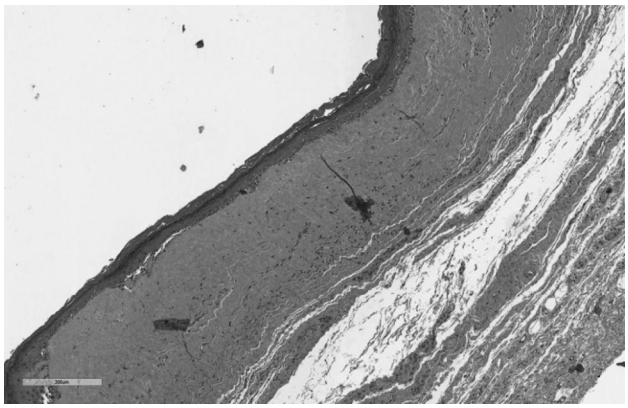

Figure 3. — Pre-treatment Histology (×10 magnification). Hyperkeratosis, dermal hypotrophy, hydropic degeneration of the basal epithelial cell, and inflammatory infiltrate of polymorphonuclear band and plasma cells.

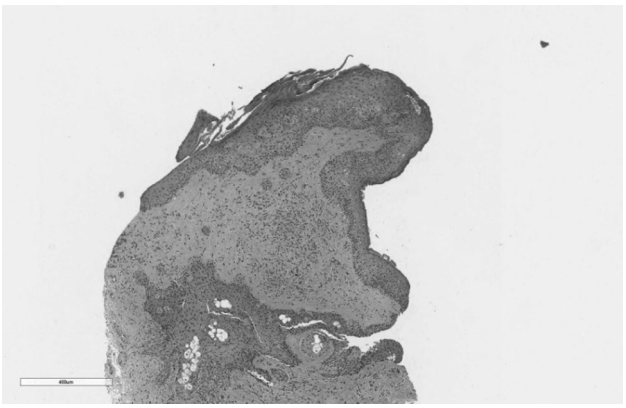

Figure 4. — Post-treatment histology (×10 magnification). Trophic epithelium with acanthosis. Lamina propria appearance is fibrillar and absent of scleral band hilaina typical of lichen, with only mild inflammatory infiltrate.

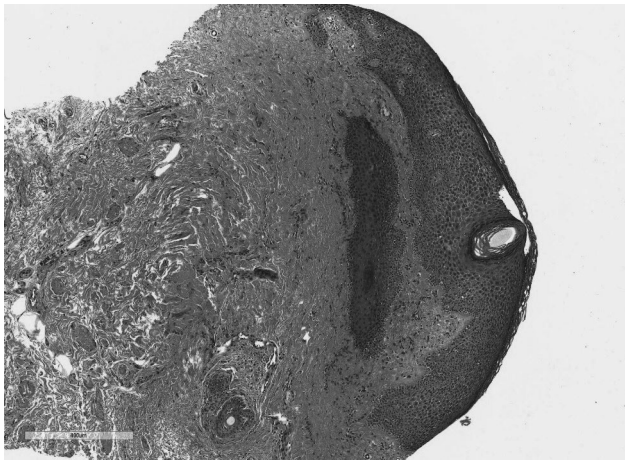

Figure 5. — Post-treatment histology (×10 magnification).Trophic epithelium without superficial hyperkeratosis. Lamina propria appearance is fibrillar with irregular spaces containing translucent materia and absent of scleral band hilaina typical of lichen.

Discussion

LS is a chronic disease diagnosed by typical characteristics, including histological signs of superficial sclerosus, hyperkeratosis, and significant epithelium thinning [3]. Until now there has no curative treatment available. Topical corticosteroids are the first choice, and improvement of symptoms becomes usually apparent within 2-3 weeks, but fail to restore histological architecture. [4]

Laser therapy has shown to be a safe and effective option that leads to clear improvement in the objective and the subjective symptoms. In the literature, mainly studies with a small number of patients can be found with mixed results. In a case series of seven women with VLS, six patients refractory to other treatment became asymptomatic following laser ablation [3]. In 1997 it was reported that CO_2 laser treatment in two women for VLS was effective in treating genital lesions, although the disease recurred. No follow-up treatment was given in these cases [7]. In 2004, Peterson *et al.* [13] treated two women with refractory anogenital LS with CO_2 laser ablation therapy with excellent surgical results. Stuart *et al.* [14] treated seven patients with LS of the vulva with CO_2 laser. In the follow-up, which ranged from 12 to 37 months, 86% of the patients were free of recurrent symptoms.

The main advantage of laser treatment is the precise ablation of affected zones in local anesthesia. With the present authors' laser resurfacing approach to VLS, they opted for high density–low energy/depth for two reasons. Firstly, LS is clinically atrophic and sclerotic, with areas of hyperkeratosis, and therefore they feel that greater coverage (density) is more important than treatment depth. The other consideration is the patients' comfort under topical anaesthesia, which may not be as easily accomplished with low density–high energy/depth parameters. The present authors feel that their selected parameters effectively obtain an equilibrium between procedural comfort, recovery time, and efficacy.

The mechanism of action of the CO_2 laser is via the absorption of light energy by water molecules within the epidermis, which leads to heat accumulation and the subsequent ablation of the epidermis and superficial dermis [14]. The fractional element of the CO_2 laser as used in this study functions by the creation of numerous microscopic thermal zones in which there is ablated skin [15, 16]. Prior to treatment, LS is histologically characterised by dermal inflammation and hyalinisation. Fractional CO_2 laser treatment not only ablates the hyperkeratotic epidermis, but also has a residual thermal effect on the underlying dermis. The dermis, especially near the dermal-epidermal junction, can theoretically be characterised by dysregulated signalling:

there is an upregulation of α3β1 integrin, which in turn stimulates MAP-kinase that promotes epidermal migration and therefore hyperkeratosis of the epidermis [2, 17].

CO_2 laser ablating the improperly functioning dermal-epidermal zone, creates a subsequent re-epithelisation characterised by the reduction of hyperkeratosis and a new zone that functions properly. This then allows for maintenance and the continued remission of LS.

Conclusion

Laser treatment is relatively simple and effective and helps patients with advanced LS and continuing symptoms, in spite of conservative therapy. The histological alterations observed in these patients, such as disintegrating fibrosis, stimulated collagen production in the lamina propria, and disappearance of the hyaline band, suggest a more comprehensive healing effect of the fractional CO_2 laser. The present authors await the next follow-up to establish the duration of the effects

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