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Comparison between a 595-nm Pulsed Dye Laser and a 1064-nm Nd:YAG Laser for Treatment of Chronic Cutaneous Lupus Erythematosus with Clinical & Histopathological Outcome Evaluation

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ABSTRACT

Background: Chronic cutaneous lupus erythematosus (CCLE) is limited to the skin, commonly affecting the face, frequently disfiguring and sometimes therapeutically challenging. Cutaneous lupus erythematosus has been treated with different laser in many studies and reports with promising results, presenting another new line of CCLE treatment.

Aim of the work: This work aimed to evaluate and compare between the efficacy and safety of pulsed dye laser (PDL) versus ND: YAG laser for CCLE treatment.

Patients and methods: This comparative study included a total of twenty patients with CCLE who had active lesion and with histologically confirmed lupus erythematosus, attending at Dermatology Outpatient Clinic of Al-Azhar University Hospitals. The patients were divided into 2 groups; group (A): 20 patients were treated by PDL and group (B): 20 patients were treated by ND:YAG laser. The degree of CCLE and clinical response evaluation was assessed using CLASI system. **Results:** In both groups A & B clearance rate was equal (50%) and Improvement rate was 100% with significant decline in ‘‘active’’ CLASI after laser treatment in both groups. P-value was 0.04 in group A and 0.005 in group B, without significant difference between both groups.

Conclusion: PDL and ND: YAG laser are safe and effective in CCLE treatment with insignificant difference between them. So, we recommend early laser usage as main treatment of CCLE particularly for refractory cases for other treatment line or as an adjunctive therapy to decrease incidence of atrophy and scarring.

Keywords: Chronic cutaneous lupus erythematosus**,** PDL, ND: YAG laser.

INTRODUCTION

Lupus erythematosus (LE) is a chronic, multisystem and autoimmune disease that has many different symptoms, CLE has three main subtypes: Acute CLE (ACLE), subacute CLE (SCLE) and chronic CLE (CCLE) [(1)].

CCLE include several presentations: Disciod LE is the commonest presentation and other variants include: hypertrophic or verrucous LE, LE panniculitis, tumid LE and chilblain lupus [(2)].

Treatments of CLE include topical and systemic corticosteroids, sunscreens, antimalarial agents, retinoids, dapsone, methotrexate, thalidomide, azathioprine, and clophosphamide. Occasionally, biologics, cyclosporin, immunoglobulins and mycophenolate mofetil have been reported [(3)]. Physical treatments for CLE include laser therapy. The efficacy of PDL and other type of laser has been shown in many studies, case reports and series [(4)].

The working mechanism of pulsed dye laser is selective photothermolysis of the cutaneous lesional blood vessels, which may modify the inflammatory process and engender improvement of CLE lesions. Therefore, PDL treatment may affect only active CLE lesion with a lesser extent atrophy and scar [(5)]. 1,064-nm ND: YAG laser treatment may be added to other therapeutic options of CCLE lesions especially when other traditional therapies have failed or are contraindicated, the selective damage of the lesion blood vessels may be the working mechanism [(6)].

Hemoglobin has highest absorption peaks from 585 to 595 nm wavelengths and another high absorption peak from 800 to 1,100 nm wavelengths [(6)].

PDL is effective to a depth of only 1 mm to 2 mm. The longer wavelength of the ND: YAG laser is better for deeper blood vessels treatment with lesser melanin absorption decreasing the risk of post inflammatory pigment alternation [(7)].

The aim of the current work was to assess and compare between the efficacy and safety of pulsed dye laser and ND: YAG laser in CCLE treatment.

PATIENTS AND METHODS

This comparative study included a total of twenty patients with active CCLE lesions with histologically confirmed lupus erythematosus, attending to Dermatology Outpatient Clinic of Al-Azhar University Hospitals, Cairo, Egypt.

Approval of the Ethical Committee and a written informed consent from all the subjects were obtained.

This study was carried out during the period between October 2014 and August 2018.

The 20 patients were divided into 2 groups; Group (A): 10 patients to be treated by PDL and Group (B): 10 patients to be treated by a 1,064-nm long-pulse ND: YAG Laser.

Inclusion criteria:

1. Patients aging 18 years or more.
2. Patients who have at least one active CLE lesion.

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3. Patients refractory to the standard regimen of therapy (e.g. topical steroids or oral antimalarial drugs) more than 4 months without clinical improvement or prefer another treatment option (e.g. poor patient compliance to topical or systemic therapy).

Exclusion criteria:

1. Age <18 years,
2. Patient doesn't have active CLE lesion.
3. Patient with systemic lupus erythematosus.
4. Patient on systemic or topical treatment for CLE (treatment should stopped at least 8 weeks before laser treatment).
5. Patient has active scalp lesion (bad prognosis).

All patients have been subjected to the following:

1. History taking & laboratory investigation.
2. Laser treatment.
3. Evaluation of clinical & histopathologic response.
4. Patient's satisfaction assessment.

History taking and laboratory investigations:

History taking included the following name, age, gender and systemic symptoms (to exclude SLE). Laboratory investigations: CBC, ESR, ANA (to exclude SLE) and Anti- dsDNA (If previous laboratory investigations are suggestive for SLE).

Laser treatment:

Twenty patients who had CCLE lesion with histologically confirmed lupus erythematosus were randomly divided into two groups. **Group A:** Patients were treated by PDL using spot size 7mm, fluence ranged from 6.5 to 8 J/cm2 and 0.5 ms pulse duration with air cooling for epidermal protection. They received 4-6 session per lesion with 1 month intervals.

Group B: Patients were treated by a 1,064-nm long-pulse ND: YAG Laser using a 5 mm spot size, a fluence of 45 J/cm2 and a pulse duration of 20 millisecond. The patients received 4-6 session per lesion with 1 month intervals.

The laser settings selected comparing previous studies with different fluences, spot sizes and pulse duration.

Clinical response evaluation:

Evaluation of the clinical response of both groups to laser treatment was assessed by two independent dermatologists at baseline, every session and one month after the last session using the CLASI system (Active CLASI), photography was taken at baseline and every session and any adverse effects were assessed.

Histopathologic response evaluation:

Punch biopsies 2.5-4 mm in diameter was taken from the lesion before laser treatment and one month after final laser treatment. For conventional light microscopy, tissue was stained with hematoxylin and eosin.

Dermatopathologist evaluated all slides blindly. Studied parameters were validated according to a semiquantitative score [absent (-), minimal (+), moderate (++), and intense (+++)]. Several parameters were evaluated: inflammatory lymphocytic infiltrate intensity, severity of vacuolar degenerative change of the basal layer (hydropic degeneration), intensity of epidermal atrophy or thinning. Other epidermal changes included Parakeratosis or hyperkeratosis and follicular plugging were classified as present or absent. Changes in blood vessels (dilatation) were evaluated and classified as absent (A), or present (P).

Patient's satisfaction assessment:

The patients assessed their satisfaction after laser treatment as very satisfied, satisfied, neither satisfied nor dissatisfied, or dissatisfied. Also, patients were asked to report any treatment side effects and pain scores using numerical analogue scales from 0 not painful, (1-3 mildly painful), (4-6 moderately painful) and (7-10 severely painful).

Statistical analysis of data:

The collected data were coded, entered, analyzed and tabulated. Analysis was done by Mann Whitney test during the present study and P value < 0.05 was considered significant.

RESULTS

In groups A & B clearance rate after laser treatment is equal (50%) and improvement rate is 100% in form of marked decrease or clearance of erythema, scaling and hypertrophy, with minimal or no improvement of atrophy and scar (fig.1-2). There is significant difference between active CLASI before and after laser treatment and no significant difference between the groups (Table 1 & 2).

Table (1): CLASI activity in each group before and after treatment

	CLASI-before			CLASI-after			
	Median	**Minimum**	**Maximum**	**Median**	**Minimum**	**Maximum**	**P value**
Group A	4	3	6	1	0	4	0.004
Group B	4	2	7	1	0	5	0.005

P≤0.05 is considered statistically significant, *analysis done by Mann Whitney test

Table (2): Comparing CLASI activity before and after treatment between the studied groups

	Group A			Group B			
	Median	**Minimum**	**Maximum**	**Median**	**Minimum**	**Maximum**	**P value**
CLASI-before	4	3	6	4	2	7	0.434
CLASI-after	1	0	4	1	0	5	0.903

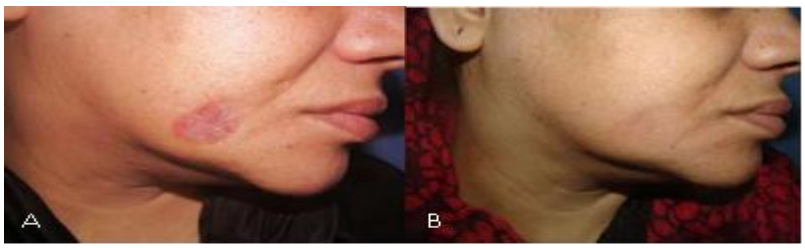

Fig (1): (A) erythema and scaling of DLE lesions affecting left cheek **(B)** clearance of DLE lesions following PDL treatment.

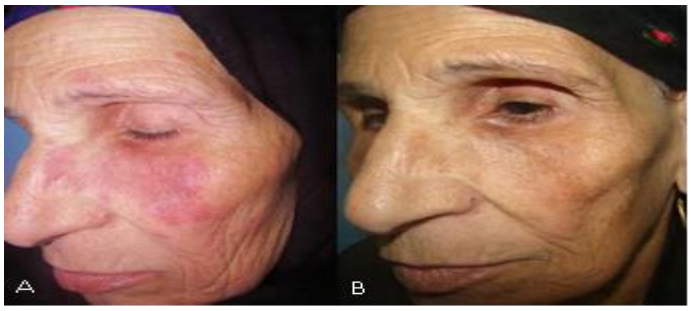

Fig (2): (A) erythema and scaling of DLE lesions affecting forehead and cheek **(B)** clearance of DLE lesions with post inflammatory hyperpigmentation following ND: Yag laser treatment.

In groups A & B Improvement of pathological characteristic of LE in form of hyperkeratosis/Parakeratosis, marked decrease of inflammatory cell infiltrates. Blood vessels dilatation, vacuolar degeneration of basal cell layer and basement membrane thickening were much improved after laser treatment, with minimal or no improvement of epidermal thinning (fig.3-4).

Table (3): Comparing histopathological changes before and after treatment between both groups

Before treatment		Group A		Group B		
		Count	Column N %	Count	Column N %	
parakeratosis or hyperkeratosis		2	20.0%	0	0.0%	0.474
		8	80.0%	10	100.0%	
Follicular Plugging		5	50.0%	5	50.0%	1.000
		5	50.0%	5	50.0%	
Epidermal Thinning		1	10.0%	0	0.0%	1.000
		9	90.0%	10	100.0%	
Vascular degeneration		10	100.0%	10	100.0%	
Inflammatory Lymphocytic infiltrate		10	100.0%	10	100.0%	
Blood vessels Changes		4	40.0%	3	30.0%	1.000
		6	60.0%	7	70.0%	
BM thickening		10	100.0%	2	20.0%	**0.001**
		0	0.0%	8	80.0%	
After treatment						
parakeratosis		10	100.0%	7	70.0%	0.211
		0	0.0%	3	30.0%	
Follicular Plugging		7	70.0%	5	50.0%	0.650
		3	30.0%	5	50.0%	
Epidermal Thinning		1	10.0%	0	0.0%	1.000
		9	90.0%	10	100.0%	
Vascular degeneration		8	80.0%	7	70.0%	1.000
		2	20.0%	3	30.0%	
Inflammatory Lymphocytic infiltrate		3	30.0%	2	20.0%	1.000
		7	70.0%	8	80.0%	
blood vessel s changes		2	20.0%	3	30.0%	1.000
		8	80.0%	7	70.0%	
BM thickening		10	100.0%	5	50.0%	**0.033**
		0	0.0%	5	50.0%	

Table (3) showed comparison between the two groups as regard histopathological changes between groups before and after laser treatment, there was no significant difference except for basement membrane thickness.

Table (4): Comparing histopathologic changes before and after PDL treatment in group A

Group A		Before treatment		After treatment	
		Count	%	Count	%
Parakeratosis or hyperkeratosis	A	2	20.0	10	100.00%
	p	8	80.0	0	0.00%
Follicular Plugging	A	5	50.0	7	70.00%
	P	5	50.0	3	30.00%
Epidermal Thinning	-	1	10.0	1	10.00%
	+	6	60.0	9	90.00%
	++	3	30.0	0	0.00%
Vacuolar degeneration	-	0	0.0	8	80.00%
	+	3	30.0	2	20.00%
	++	7	70.0	0	0.0%
Inflammatory Lymphocytic inflitrate	-	0	0.0	3	30.00%
	+	0	0.0	7	70.00%
	++	2	20.0	0	0.0%
	+++	8	80.0	0	0.0%
Blood vessels Changes	A	4	40.0	2	20.00%
	P	6	60.0	8	80.00%
BM thickning	A	10	100.0	10	100.00%
	P	0	0.0	0	0.00%

Table (4) showed histopathologic changes before and after PDL treatment in group A.

Table (5): Comparing histopathological changes before and after ND: YAG laser treatment in group B

Group B		Before treatment		After treatment	
		Count	%	Count	%
Parakeratosis	A	0	0.0	7	70.00%
	P	10	100.0	3	30.00%
Follicular plugging	A	5	50.0	5	50.00%
	P	5	50.0	5	50.00%
Epidermal Thinning	_	0	0.0	8	8.00%
	+	7	70.0	2	20.00%
	++	3	30.0	0	0.00%
Vacular degeneration	_	0	0.0	7	70.00%
	+	8	80.0	3	30.00%
	++	2	20.0	0	0.0
Inflammatory Lymphocytic inflitrate	_	0	0.0	2	20.00%
	+	3	30.0	8	80.00%
	++	4	40.0	0.0	0%
	+++	3	30.0	0.0	0%
blood vessel s changes	A	3	30.0	4	40.00%
	P	7	70.0	6	60.00%
BM thicknening	A	2	20.0	5	50.00%
	p	8	80.0	5	50.00%

Table (5) showed histopathologic changes before and after ND: YAG laser treatment in group B.

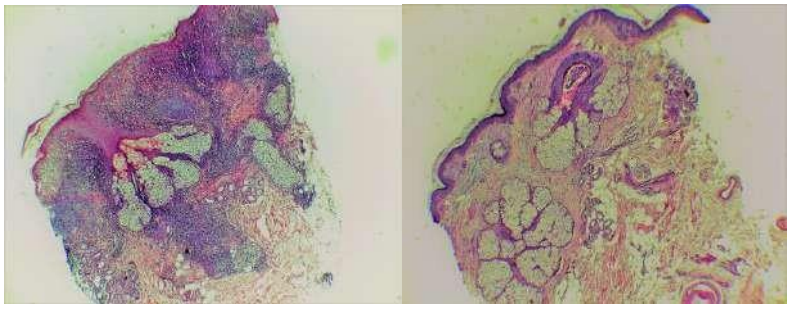

Fig (3): (A) showed hyperkeratosis, epidermal thinning, vacuolar degeneration, extensive inflammatory infiltrate mostly perifollicuar & periadenexal and dilated blood vessel representing the histopathologic changes of DLE. **(B)** showed normalization of stratum cornium (basket wave pattern), improvement of epidermal thinning, vacuolar degeneration and disappearance of inflammatory infiltrate after PDL treatment.

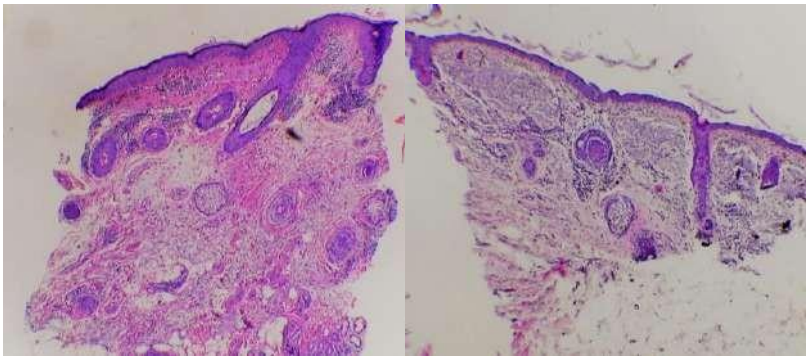

Fig (4): (A) showed hyperkeratosis, epidermal thinning, vacuolar degeneration, basment membrane thickening and inflammatory infiltrate perifollicuar & periadenexal representing the histopathologic changes of DLE. **(B)** showed remaining of epidermal thinning, improvement of vacuolar degeneration, basement membrane thickening and inflammatory infiltrate after ND: Yag laser treatment.

DISCUSSION

Laser therapy has been used to treat CLE, mostly in cases of DLE. More than fourteen published studies and case reports with different types of laser especially PDL have described successful treatment of various type of CLE with few side-effects [8].

This comparative study was carried out on 20 patients with histologically confirmed cutaneous lupus erythematous. Clinical diagnosis was supported by serological examinations to exclude SLE. The patients were divided randomly to 2 groups: group A (Patients were treated by PDL) and group B (Patients were treated by ND: YAG laser). All patients had CCLE (19 patients with DLE and one patient with tumid LE) active lesions located on the face except one patient had also chest lesion.

The present study showed significant decline in active CLASI after PDL and ND: Yag laser treatment of CCLE in both groups without significant difference in between the studied groups. In both groups 50% complete clearance and 100% improvement of CCLE lesions was obtained. The most beneficial results were obtained with erythema and scaling with variable degrees of improvement for other DLE component. This finding meets study conducted by **Raulin *et al.*** [9] reported a clearance rate of around seventy percent in patients with CLE (nine of them with DLE) after pulsed dye laser treatment while two patients developed postinflammatory hyperpigmentation. **Brauer *et al.*** [8] **reported that** pulsed dye laser (PDL) has been used in eight studies. In studies conducted by **Diez *et al.*** [10] **Truchuelo *et al.*** [11] reported that 12 of 19 patients had complete clearance of their cutaneous lesions (including 12 tumid LE and 5 DLE patients) with marked decrease in size, erythema, and edema of their skin lesions. In the third prospective study conducted by **Erceg *et al.*** [12] on twelve patients with DLE, after PDL treatment, there was statistically significant decrease in CLASI. Other case series conducted by **Baniandres *et al.*** [13] reported successful usage of PDL for 14 patient with cutaneous LE (including eight patients with DLE). They obtained an average clearance rate of over 60%. Finding for group (B) meets result for case study conducted by **Park *et al.*** [6] of refractory DLE patient was successfully treated using ND: YAG laser with significant satisfactory results.

This was the first study to compare PDL with ND: YAG laser in treatment of CCLE. Comparing ND: YAG laser to PDL because of its efficacy that is very similar to that of the PDL in treatment of some vascular lesion. Both of them have been used separately in clinical trials for CCLE treatment with promising results. ND: YAG laser is known to be less painful and safer for darker-skinned patient**. Alam *et al.*** [14]

compared the effectiveness and tolerability of PDL and ND: YAG laser for treatment of diffuse facial erythema, they found both treatments had improved erythema. PDL was found to be significantly more effective, however ND: YAG laser was less painful and might be safer for darker skin type patients.

In the current study, eighty five percent of the patients had tried several therapies, topical corticosteroid and some had also been treated with systemic antimalarial or systemic steroids. They were refractory to previous treatments and some of them already developed scars and atrophy. This finding meets study conducted by **Ekbäck** and **Troilius** [(15)] who found that PDL are efficient and safe treatment for early lesions of CLE as well as patients who were refractory to previous treatments. Also, successful treatment of DLE patient refractory to conventional treatment was reported to be using ND: YAG laser in a study conducted by **Park *et al.*** [(6)].

In the current study dark-skinned patients had more laser sessions and with increasing incidence of post inflammatory hypo/hyper pigmentation. This could be explained by competition between melanin and oxyheamoglobin to absorb visible light so in patients with darker skin types, this could affect efficacy and increase incidence of side-effects hence the need of more sessions [(16)].

As regards side effect, 13 patients of both groups (65%) developed post inflammatory hypo/hyperpigmentation most of them was transient. This finding was mainly noticed in patients with darker skin types and patient had atrophy. This is matching the results of other studies conducted by **Baniandres *et al.*** [(13)]**; Erceg *et al.*** [(12)] and **Raulin *et al.*** [(9)] but with higher percentage in current study that might be related to darker skin type of our patient and without insignificant difference between both groups. Also, in a study conducted on 62 Egyptian patients with DLE have been treated with PDL, 17 patients (85%) had transient hyperpigmentation and 3 patients (15%) had hypopigmentation [(16)].

As regards pain ratings in both groups, pain rating was higher in PDL group but with insignificant difference. Pain was not a limiting factor with either treatment. This finding could be explained by that patient who received laser for treatment purpose not for cosmetic concern could tolerate pain more, especially with desperate patient who had gone through many other treatments without improvement.

In the current study, we noticed that scars and atrophy in some patients of both groups improved after laser treatment but lesser than other component of CLE lesion and not in all patients. This finding meets study conducted by **Soliman *et al.*** [(16)] including twenty-two patients with DLE scar, only one patient showed complete resolution of the scar while other patients showed different degrees of improvement. Thermal damage to abnormal collagen may lead to collagen remodeling. This could explain the improvement of scars and atrophy of some patients in this study after laser treatment. While, improvement of early scar rather than old one could be explained by that chronic scar tissue (more than one year) affect the penetration depth of the laser and decrease number of targeted blood vessels.

In the present study, there was no exacerbation or worsening of CCLE lesions in patients treated by PDL (visible light spectrum) or ND: YAG laser (infrared light spectrum) in both groups. This could be explained by association of LE with cutaneous photosensitivity after ultraviolet exposure not visible or infrared light and pathogenesis might be related to ultraviolet-mediated cell apoptosis, chemokine and cytokine dependent processes. **Kuhn *et al.*** [(17)] showed that there are no published reports of lupus erythematosus exacerbation or photosensitivity in patient following PDL treatment [(18)].

In the current study, after PDL and ND: YAG laser therapy, post-treatment biopsies were performed to compare with pre-treatment biopsies. We observed marked improvement of hyperkeratosis, perifollicular, periadenixal inflammatory infiltrate, liquefactive degeneration of basal cell layer, variable degrees of epidermal thinning and basement membrane thickening improvement. This finding meets studies conducted by **Yélamos *et al.*** [(18)] who found improvement of histopathologic changes of LE after PDL treatment. This results were correlated with the similar good clinical results.

CONCLUSION

It could be concluded that both of PDL and ND: YAG laser have significant effect in treatment of CCLE with minimal side effect without significant difference in between. So, laser could be used as main treatment of CCLE particularly for refractory cases for other treatment line or as an adjunctive therapy to decrease incidence of atrophy and scarring.

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