308-nm excimer laser plus topical calcipotriol in the treatment of vitiligo; A single blind randomized clinical study

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Background: There is a large variety of therapeutic agents for the treatment of vitiligo, but it still remains a challenge. Narrow-band UVB phototherapy and 308-nm excimer laser have been shown to be safe and effective for the treatment of vitiligo. Topical calcipotriol has recently been reported to enhance the efficacy of phototherapy, especially 8-methoxypsoralen plus UVA (PUVA). The goal of this study was to evaluate whether the addition of topical calcipotriol enhances the efficacy of 308-nm excimer laser in the treatment of vitiligo.

Methods: The patients with symmetrical vitiliginous lesions received 308-nm excimer laser plus Calcipotriol ointment 0.005% (Daivonex®) as the intervention group and 308 nm excimer laser plus vaselin as the control group on the lesions of the right side. All patients in the two groups applied vaselin on the lesions of the left side. The evaluation of the patients was performed at baseline and at 12th week (the last laser session). SPSS version 15.0 package software was used for statistical analysis. P-values< 0.05 were accepted as statistically significant.

Results: Seventy out of 83 patients completed the study. The diameter of the right side lesions (308nm excimer laser + calcipotriol) changed from 27.21 cm^2 to 15.82 cm^2 in the intervention group and from 27.86 cm^2 to 16.02 cm^2 in the control group; This difference was not statistically significant (p-value=0.74).

Conclusion: Our findings showed that 308-nm excimer laser was effective and safe in the treatment of vitiligo, and that topical calcipotriol had no additive or synergistic effect.

Keywords: 308-nm excimer laser, topical calcipotriol, phototherapy, vitiligo

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INTRODUCTION

Vitiligo is a worldwide disease with a prevalence of about 1-3%. There is a large variety of therapeutic agents, but its treatment still remains a challenge [1-4]. There is no consensus regarding its etiology, but there are different hypotheses for its pathogenesis such as cellular autoimmunity, oxidative stress, melanocytorrhagy, heredity and neural factors. Based on the supposed etiologies, different treatment options have been tried and approved, meaning that molecular and cellular mechanisms hold the key for various therapeutic agents used. A better understanding of vitiligo repigmentation provides new alternatives and enhances the efficacy of current treatments [5].

Phototherapy including PUVA, broad band UVB, narrow band UVB (the preferred form of phototherapy for the treatment of vitiligo) and 308-nm excimer laser (emit focused wavelength

adjacent to NBUVB 311-nm) are immunomedulator agents and stimulators of the melanocyte precursors; therefore, they are proper options for the treatment of vitiligo [6]. Based on the etiopathomechanisms of vitiligo, adjunctive agents combined with phototherapy, with the purpose of efficacy enhancement and minimizing their long-term side effects such as carcinogenecity, have been suggested. Calcipotriol, which is a synthetic analog of vitamin D_3, is one of them. It causes proliferation, activation and migration of melanocytes as well as modifying T-cell activation. At the molecular level, combination of calcipotriol with different forms of phototherapy and 308-nm excimer laser can decrease lesion progression in vitiligo by immunosuppression, and possibly induce repigmentation by activating melanocyte precursors and melanogenic pathways synergistically. There are some studies which have shown enhancement of PUVA and NBUVB efficacy when calcipotriol was added, but no improvement has been reported in outcomes in other studies [7-11]. To our knowledge, there is only one report in the literature; this report failed to show the synergistic effect of the combination of calcipotriol and 308 nm excimer laser in the treatment of vitiligo [5]. To date, it has been impossible to explain the contrast between the convincing results of molecular research and the results of such clinical studies, thus, the necessity of precise clinical studies is felt to explain such differences and find more efficient therapies. Therefore, we decided to determine whether calcipotriol could enhance the efficacy of 308nm excimer laser in the treatment of vitiligo in a randomized clinical trial.

PATIENTSS AND METHODS

Patients

This randomized, controlled, prospective, right/left comparative and single blinded clinical trial study was done in the laser clinic of Behsima Center, Tehran, Iran, between May 2007 and May 2009.

Inclusion criteria were generalized vitiligo for at least one year or stable vitiligo in all skin color phenotypes. Exclusion criterion were pregnancy, lactation, allergy to calcipotriol, renal insufficiency, abnormality of bone or calcium metabolism, light-sensitive dermatoses, photodermatoses, phototoxic systemic or topical medication(s), previous history of arsenic exposure, excessive exposure to UV light and previous history of skin cancer.

The study was approved by the Ethics Committee under the supervision of vice-chancellor for Research of Tehran University of Medical Sciences. Treatment approach, duration of treatment and possible complications were explained to the patients. All patients signed the informed consent form.

Treatment protocol

Included patients with symmetrical vitiliginous lesions were randomized into 2 groups. The intervention group received 308-nm excimer laser plus Calcipotriol ointment 0.005% (Daivonex®) on the lesions of the right side of the body and the control group received 308 nm excimer laser plus vaselin on the lesions of the right side.

All patients in both groups administered vaselin on the lesions of the left side. Excimer laser was used two times weekly for 12 weeks. The average initial dose was 50 mJ/cm2.The incremental dose was 50 mJ/cm^2 at each exposure. If there were moderate to severe erythema, irritation or itching, therapy was suspended until the complication was resolved; then, the dose of the laser decreased by 20% of the last session dose. If severe and non resolving complications happened, that patient left the study and received proper treatment prescribed by a dermatologist. Calcipotriol ointment 0.005% (Daivonex®) and vaselin were used 2 times daily.

Efficacy assessments

The evaluation of the patients was performed at baseline and at 12th week (the last laser session). At each evaluation, all lesions were photographed and visual scale software was used for comparing the diameter of the lesions before and after treatment in each group. Also, response rate (percentage of repigmentation) was scored (Table 1).

Table 1. Repigmentation rate and response score

Repigmentation Rate %(RR)	Response interpretation	Score
RR ≤1	No response	0
1< RR ≤25	Mild response	1
25< RR≤ 50	Moderate response	2
50< RR≤75	Good response	3
75< RR≤100	Excellent response	4

The score of repigmentation and the side effects in each evaluation were documented in pre-designed forms for each patient.

Statistical analysis

SPSS version 15.0 package software was used for statistical analysis. Outcomes of groups were compared with T test. P-values< 0.05 were considered statistically significant.

RESULTS

A total of 83 patients (42 females and 41 males) with bilateral symmetrical vitiliginous lesions were included in this study in a period of 2 years, from May 2007 to May 2009. Among them, 13 patients did not complete the study for unknown reasons. Seventy patients, 36 females (51.43 %) and 34 males (48.57%), completed the study. All patients were divided into 2 groups, intervention group (35 patients) and control group (35 patients) through blocked randomization (Figure 1). Baseline demographic and clinical characteristics of each group are detailed in Table 2.

The number of the patients with the response rate scores of 0 (no response), 1 (mild), 2 (moderate), 3 (good) and 4 (excellent) was 1 (2.8%), 3 (8.5%), 19 (54.2%), 10 (28.5%) and 2 (5.7%) in the intervention group and 3 (8.5%), 4 (11%), 16 (45.7%), 9 (25.7%) and 3 (8.5%) in the control group (right side lesions), respectively (Figure 2).

In other words, 31 patients in the intervention group (308 nm excimer laser + calcipotriol) and 28 patients in the control group (308 nm excimer laser + vaselin) were clinical responders (scores 2,3,4). The details of the clinical response rates of right side lesions of each group, considering sex,

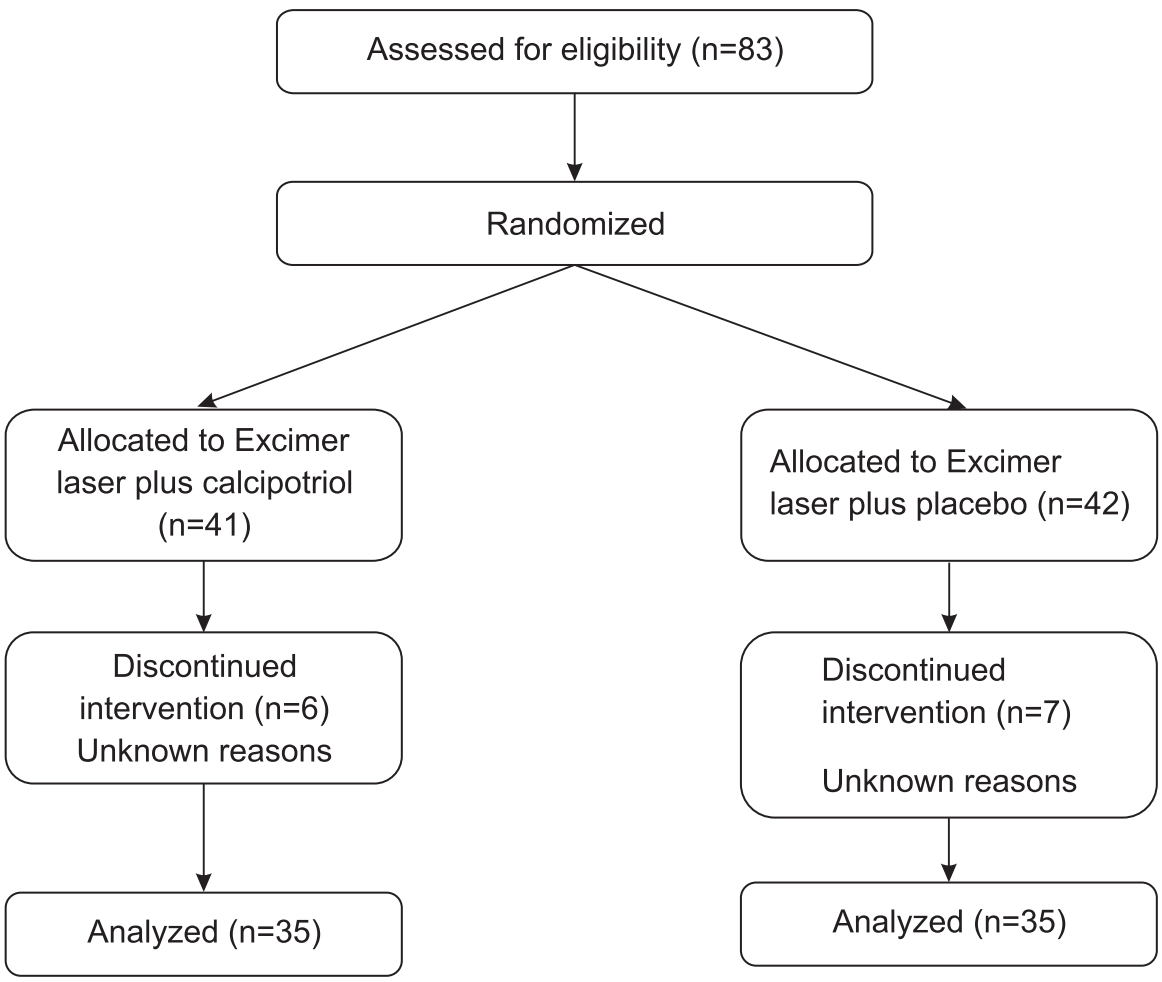

Figure 1. Consort Flow Diagram

Table 2. Baseline demographic and clinical characteristics

	Intervention group patient No.	Control group Patients No.
Patients	35	35
Sex		
Female	11	25
Male	24	10
Age		
Mean	34	31
Range	18-46	18-42
Vitiligo duration		
1-2years	28	21
3-5years	6	10
>5years	1	4
Skin phenotype		
I	0	0
II	8	7
III	16	18
IV	11	10
Previous treatment		
Topical corticosteroid	10	10
NBUVB	3	5
PUVA	3	8
Elidel	5	5
Tacrolimus	0	0
Excimer laser	2	3
Anatomical		
Head & neck	7	13
Trunk	9	12
Upper limb (proximal)	4	2
Upper limb (distal)	4	2
Lower limb (proximal)	8	4
Lower limb (distal)	3	2

duration of disease, skin phenotype and anatomical location, are shown in Table 3.

As Table 3 shows, sex, duration of disease, skin phenotype and anatomical location of right side lesions did not affect the number of clinical responders (scores 2,3,4) in 2 groups significantly.

Spontaneous resolving of lesions was considered as a confounding factor, and for determining its effect, diameter changes of left side lesions that only received vaselin were evaluated in both groups; the changes were from 27.28cm^2 to 26.4cm^2 in the intervention group and from 26.45cm^2 to 26.45cm^2 in the control group but the differences were not significant in each group (p-value=0.95 in the intervention group and p-value=1.00 in the control group). The diameter of the right side lesions in the intervention group (308nm excimer laser + calcipotriol) and the control group

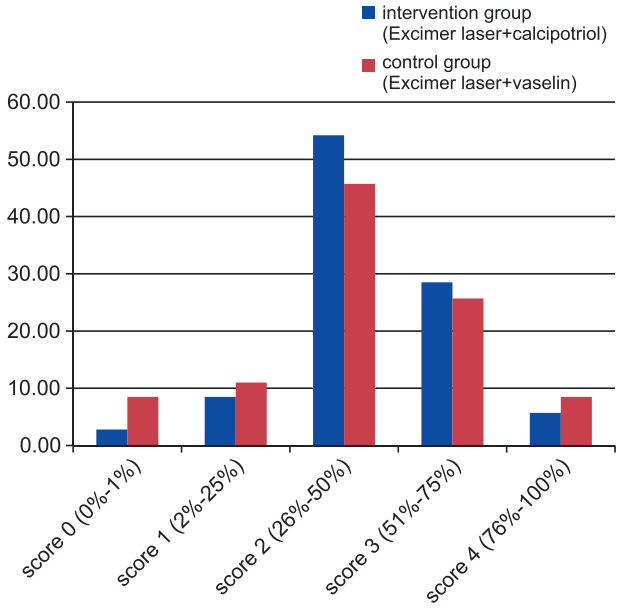

Figure 2. Percentage of patients with different repigmentation rates in each group after 12 weeks

changed from 27.86 cm^2 to 16.02 cm^2 and from 27.21 cm^2 to 15.82 cm^2, respectively. The diameter changes were statistically significant in each group (p-value<0.001).

The adverse reactions were erythema and pruritus; all were mild. There were no significant differences in side effects between 2 groups. No patient left the study due to side effects.

For determining the main goal of this study, diameter changes of right side lesions in the intervention group (308nm excimer laser plus Calcipotriol),11.84 cm^2, was compared to the control group (308nm excimer laser plus vaselin), 11.39 cm^2, but the difference was not significant (p-value=0.74).

DISCUSSION

Despite various therapeutic agents for vitiligo, its treatment still remains unsatisfactory. To date, one of the most established treatments is NBUVB. The slow response of vitiliginous lesions on one hand and worsening of their appearance initially, when treated with NBUVB due to tanning of the surrounding skin on the other, have encouraged dermatologists to use a focused and high dose light (308-nm excimer laser) on the affected skin and try different combinations to find a synergistic effect with the purpose of avoiding photodamaging of

Table 3. Treatment outcome

	Intervention group*	Control group*	P-value
Sex			
Female	9/11 (81.8%)	21/25 (84%)	0.11
Male	22/24 (91.6%)	7/10 (70%)	
Duration of disease			
1-2 years	27/28 (96.4%)	18/21 (85.7%)	
3-5 years	4/6 (66.6%)	8/10 (80%)	0.78
>5 years	0/1 (0%)	2/4 (50%)	
Skin phenotype			
I	0/0 (0%)	0 (0%)	
II	7/8 (87.5%)	6/7 (85.7%)	0.20
III	15/16 (93.7%)	16/18 (88.8%)	
IV	9/11 (81.8%)	6/10 (60%)	
Anatomical location			
Head & neck	7/7 (100%)	12/13 (92.3%)	
Trunk	9/9 (100%)	11/12 (91.6%)	
Upper limb (proximal)	3/4 (75%)	1/2 (50%)	0.55
Upper limb (distal)	3/4 (75%)	1/2 (50%)	
Lower limb (proximal)	6/8 (75%)	2/4 (50%)	
Lower limb (distal)	2/3 (66.6%)	1/2 (50%)	

*Clinical responders No. (score2, 3, 4)

the unaffected skin and achieving the response more rapidly. Despite the small skin carcinogenicity risk of any UVB therapy, the real risk of excimer laser still remains unknown, so caution should be taken. Considering molecular mechanisms, different combinations with phototherapy (PUVA, NBUVB, and excimer Laser) have been tried in the treatment of vitiligo [6-11]. While Sassi et al, showed the efficacy of topical hydrocortisone 17-butyrate cream in enhancing the effect of excimer laser in the treatment of vitiligo of the face and neck [12] and Kawalek et al, showed the efficacy of topical tacrolimus plus excimer laser [13], others decided to try the combination of calcipotriol with phototherapy. Goldinger et al, 2007, in a non randomized single blind study containing 10 patients, showed that calcipotriol 2 times daily did not enhance the efficacy of excimer laser (3 times weekly) in the treatment of vitiligo [14]. According to our study, calcipotriol did not enhance the efficacy of excimer laser in the treatment of vitiligo. This conclusion was achieved according to diameter changes in intervention and control group lesions and removing the effects of the confounding factors, although not significant.

However, we may have reached this conclusion because we used 308 nm excimer laser plus calcipotriol schedule, our timing or our preparation; therefore, different types of regimen schedules should be tried to determine the real effect of vitamin D derivatives on enhancing excimer laser efficacy in the treatment of vitiligo. To our knowledge, this was the first phase 2 randomized clinical trials done to investigate whether topical calcipotriol enhances 308-nm excimer laser efficacy in the treatment of vitiligo. In conclusion, our study showed that combination of excimer Laser with calcipotriol did not produce a superior result in the treatment of vitiligo than did excimer laser alone.

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