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A preliminary study of fractional CO₂ laser added to topical tacrolimus combined with 308 nm excimer lamp for refractory vitiligo

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Abstract

Fractional CO₂ laser has been proposed recently to be effective and well tolerated in patients with refractory vitiligo. In this preliminary, prospective study, 21 patients with multiple, localized, refractory, non-segmental vitiligo lesions were randomized to receive either tacrolimus ointment plus 308 nm excimer lamp (control), with or without the addition of fractional CO₂ laser. There was no statistically significant improvement in the repigmentation on the laser side compared to the control side. Treatment was generally well-tolerated; only localized adverse effects were noted. Overall the triple combination therapy was not superior to tacrolimus ointment plus 308 nm excimer lamp. Treatment failure may reflect insufficient penetration of tacrolimus ointment through the holes created by fractional CO₂ laser on the skin.

Keywords

laser; therapy-topical; vitiligo

1 | INTRODUCTION

Vitiligo is the most common disorder causing hypopigmentation of the skin and mucous membranes. As many patients with vitiligo remain resistant to conventional treatment, combination treatment strategies have become a focus of interest. The present study was based on the widespread use of topically applied tacrolimus ointment plus 308 nm excimer lamp for vitiligo, and tested the additional combination with fractional CO₂ laser. Topical tacrolimus is reported to have good efficacy for repigmentation in vitiligo (Sisti et al., 2016). The fractional CO₂ laser creates microscopic vertical holes within the tissue (Hædersdal et

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CONFLICT OF INTEREST

There is no conflict of interest to declare.

al., 2010). These microchannels could facilitate penetration of topically applied drugs such as tacrolimus, and this approach was tested in the combination treatment of refractory vitiligo (Elzawahry, Zaki, Wissa, & Saleh, 2017; Li et al., 2015). There have been no reports regarding the use of fractional CO₂ laser plus tacrolimus ointment plus 308 nm excimer lamp in the treatment of localized, refractory, non-segmental vitiligo. This was a small, exploratory, prospective study in patients with multiple treatment-resistant lesions over 6 months. Individual lesions on patients were randomized to receive either the triple combination therapy or the double therapy.

2 | MATERIALS AND METHODS

The present study was approved by the Institutional Review Board of West China Hospital of Sichuan University, Chengdu and was in accord with the Helsinki Declaration. A form of informed consent was signed. Twenty-one patients with localized, non-segmental vitiligo lesions were included. All patients had refractory lesions with no improvement having taken place, despite receiving more than 1 year of conventional treatment. Patients with unstable lesions within the preceding 1 year, a history of keloids, and pregnant or breast-feeding women were excluded. Two separate lesions in the same body site were randomly assigned to receive one of the two types of combination treatment: Group 1 lesions, received fractional CO₂ laser followed by 0.1% tacrolimus ointment plus 308 nm excimer lamp; Group 2 lesions, received 0.1% tacrolimus ointment plus 308 nm excimer lamp.

Three sessions of 10,600 nm fractional CO₂ laser (GuoXiong, Chengdu, China) were performed at 1-month intervals in treatment Group 1. The treatment settings were: pulse energy of 100 mJ, a spot density of 100 spots per cm², static mode, two passes. 0.1% tacrolimus ointment (Protopic®; Astellas Pharma Inc., Takaoka, Japan) was applied twice daily without occlusion. A 308 nm excimer lamp (AlmaLaser Ltd, Caesarea, Israel) was administered twice weekly. The protocol of 0.1% tacrolimus ointment and 308 nm excimer lamp was the same for lesions in treatment Groups 1 and 2 and lasted for 6 months.

During the pretreatment visit and at 6 months after enrollment, photographs were taken, and were assessed by two blinded dermatologists using a repigmentation grading scale as reported in previous studies (Shin, Lee, Hann, & Oh, 2012; Abdel & Ibrahim, 2015): no improvement; minimal improvement (1–25%); mild improvement (26–50%); moderate improvement (51–75%); excellent improvement (>75%). Moreover, the subjective clinical satisfaction of each patient was assessed using a 10-point visual analog scale (VAS) ranging from 0–10. Zero was defined as “not satisfied at all” and 10 was defined as “completely satisfied”. The Wilcoxon signed-rank test was used to compare treatment Group 1 and treatment Group 2. Any adverse events were noted.

3 | RESULTS

The clinical features of the treated patients are reported in Table 1. Most lesions (85.7%) in the patients showed some repigmentation, but there were no differences between different treatment sides, according to the physicians' evaluations (Table 2). Regarding patient satisfaction, there was no significant difference ($p > .05$). Sixteen patients experienced

minimal to moderate improvement on both sides; with excellent improvement in two patients (Figure 1). All patients reported pain and burning sensation during the laser treatment, but in general, the erythema and edema had disappeared within 1 hr after the treatment. Posttreatment crusting was noted in all patients after laser, and had disappeared by 7–10 days later. Erythema and peri-lesional hyperpigmentation were observed in some laser-treated patches, which reduced afterward. No other long-lasting side effects were observed.

4 | DISCUSSION

Human skin acts as a protective barrier, and there are physicochemical limitations to the amounts of topical drugs that can traverse the cutaneous barrier. The therapeutic efficacy of topical drugs relies on their capacity to penetrate the superficial skin layers and gain entry to the targeted cells. The major rate-limiting step for percutaneous absorption is passage across the stratum corneum (Morrow, Garland, Woolfson, & Donnelly, 2007). Modalities have been designed that can introduce pores or channels into the skin, that may be “opened” sufficiently wide to enable topically applied drugs to pass through them and to penetrate into the skin. For instance, laser-assisted dermabrasion was introduced for refractory vitiligo. The fractional CO₂ laser creates microscopic vertical canaliculi known as “microscopic treatment zones” (MTZ), leading to a fractional disruption of the epidermal barrier, which will allow the penetration of certain topically applied drugs. Studies have shown that the treatment with fractional CO₂ laser combined with topical betamethasone or salicylic acid could effectively and safely be used in the treatment of vitiligo (Cunha, Scabine, Bonati, & Salai, 2016; Li et al., 2015). However, our study suggests that the triple treatment failed to achieve superior repigmentation or better patient satisfaction. We suggest that the reasons for the relative treatment failure are as follows.

Firstly, the “500 Dalton rule” lays down, that drug molecules with a molecular weight larger than 500 Da show a rapid decline in skin absorption (Bos & Meinardi, 2000). In previous studies, the topical drugs that were combined with fractional CO₂ laser all had a molecular weight under 500 Da, making them more likely to penetrate the skin than tacrolimus (mol wt = 822 Da). Moreover, reports have shown highly variable absorption of topical tacrolimus (Pople & Singh, 2013).

Secondly although many studies have demonstrated the microscopic channels formed after fractional CO₂ laser, can reach as far as the deep dermis as shown by histological studies (Beltraminelli, Dietrich, & Hunziker, 2011; Elman, Fournier, Barnā, Bernstein, & Lask, 2016; Grunewald et al., 2011). Therefore theoretically, tacrolimus ointment could penetrate down to the targeted skin layer through these holes. However in our patients, the patches of skin that had been treated with fractional laser were all covered by a thin crust that lasted for 7–10 days after each laser treatment. This crust is likely to have impeded the absorption of tacrolimus ointment that was applied on top of the crust, rather as a surface “coat”. It has been reported that the epidermis regains its normal structure, after 3 days have elapsed post-fractional CO₂ laser. The final remodeling of the skin is complete by Day 14 (Grunewald et al., 2011). Therefore the application of tacrolimus may not have taken place at the optimum timing for absorption.

Thirdly, the perilesional zone of tissue necrosis that occurs around the microholes might hamper the drug penetration as well. Numerous observations have shown that the healing process occurring after fractional CO₂ laser can induce various kinds of cytokines and growth factors, and might contribute to mitogenic stimulation for melanocytes (Shin et al., 2012). However this may be insignificant compared with the known synergistic activity of topical tacrolimus plus 308 nm excimer lamp leading to activation of melanocyte mitogenesis, melanocyte migration and melanogenesis (Ba, James, Spencer, & Phelps, 2004), all of which induce a fairly rapid clinical response in vitiligo. Moreover the crust caused by the fractional laser, may have impeded the penetration of the tacrolimus, thus canceling out the beneficial effects of the laser. Considering all these factors, fractional CO₂ laser failed to exert an additive effect in enhancing the degree of repigmentation in vitiligo.

5 | CONCLUSION

Our results were based on a relatively few number of patients with refractory vitiligo lesions, so the utility of fractional CO₂ laser combined with different topical drugs should be further addressed in the future. As all patients were treated with the combination of both tacrolimus ointment and 308 nm excimer laser, it is unclear which treatment had the most important effect. Whether the clinical use of fractional CO₂ laser for refractory vitiligo, in combination with any other modalities, has a role to play remains uncertain.

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FIGURE 1. Photograph of patient. Note: (a and b) pretreatment; (c and d) 6 months posttreatment; (c) treatment side; (d) control side

TABLE 1

Summary of patient characteristics

Patient characteristics	
Gender, <i>n</i> (%)	21 (100)
Male	13 (61.9)
Female	8 (38.1)
Lesion site, <i>n</i> (%)	
Face	3 (14.3)
Torso and limbs	7 (33.3)
Hands and feet	11 (52.4)
Disease duration, months	7.6 ± 6.3
Fitzpatrick skin type, <i>n</i> (%)	
III	16 (76.2)
IV	5 (23.8)

TABLE 2

Comparison between treatment Group 1 and treatment Group 2 regarding degree of improvement

Degree of improvement	Group 1 (triple site) <i>n</i> (%)	Group 2 (double site) <i>n</i> (%)
No improvement	3 (14.3)	3 (14.3)
Minimal	4 (19.0)	6 (28.6)
Mild	8 (38.1)	7 (33.3)
Moderate	4 (19.0)	3 (14.3)
Excellent	2 (9.5)	2 (9.5)
<i>p</i>	.13 [*]	

^{*} Statistically significant at $p < .05$.