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Efficacy of conventional continuous vs. cyclic on-off excimer laser treatment in vitiligo

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이 논문을 의학 석사학위 논문으로 제출함.

2017 년 8 월

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감사의 글

본 논문을 완성할 때까지 물심양면으로 도움을 주시고 지도와 조언을 아끼지 않으셨던 지도교수이신 강희영 교수님께 진심으로 감사 드립니다. 또한 좋은 연구를 할 수 있도록 부족한 제게 많은 조언과 격려를 주신 김장희 교수님, 박태준 교수님께 깊은 감사의 마음을 전합니다. 그리고 연구 기간 동안 도움을 주신 피부과학교실의 모든 선생님들께 감사 드립니다.

언제나 아낌 없는 사랑으로 지원해 주시는 부모님을 비롯한 가족들에게도 깊은 감사의 마음을 전합니다.

2017 년 7 월

저자 씀

-ABSTRACT-

Efficacy of conventional continuous vs. cyclic on-off excimer laser treatment in vitiligo

OBJECTIVE: To compare the efficacy of conventional continuous excimer laser treatment and cyclic on-off scheduled excimer laser treatment in vitiligo.

DESIGN: A randomized, controlled, split-body, non-inferiority study.

SETTING: The trial was performed in two tertiary health care centers in Korea.

PARTICIPANTS: 12 patients (16 pairs of lesions) with bilateral and symmetrically distributed vitiligo and whose disease duration was less than 5 years. The patients taking systemic steroids or having enlarging lesions were excluded. All of 12 patients completed the study.

INTERVENSIONS: All lesions were treated twice weekly by excimer laser for a total of 9-month trial period: continuously in group A, or cyclically with 2-month treatment and 1-month intermission every 3 month (total 3 cycles during the trial) in group B. Topical tacrolimus 0.1% ointment was equally applied to both groups throughout the trial.

MAIN OUTCOMES AND MEASURES: Photographic documentation of lesions was conducted every month and the final degree of repigmentation of each group was assessed with a repigmentation rate (%) by using image analysis software. The non-inferiority margin was set at 10%.

RESULTS: The mean difference of repigmentation rate between group A and B was 2.194% and the 95% confidence interval (-4.982% to 9.370%) was lower than the non-inferiority margin (10%). In group B, neither loss of repigmentation nor worsening of the vitiligo lesions was observed during intermission.

CONCLUSIONS AND RELEVANCE: The cyclic on-off excimer laser treatment was as effective as the continuous excimer laser treatment in vitiligo. It can be a new

treatment strategy for vitiligo without deteriorating the disease.

Keyword: vitiligo, excimer laser, UVB treatment, cyclic treatment, melanocyte exhaustion

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF TABLES

INTRODUCTION

308-nm xenon chloride excimer laser (EL) has been widely used in treating localized vitiligo (Zhang et al., 2010). The EL treatment is usually given two or three times weekly as long as ongoing repigmentation is observed (Hofer et al., 2005; Park et al., 1995). Although it showed quick excellent repigmentation in some patients, it generally requires long treatment durations over several months to a year (Alhowaish et al., 2005).

The long-term UV irradiation induces cutaneous photoadaptive responses such as skin thickening which limits UV penetration and result in increasing minimal erythema dose (MED) of EL (Bataille et al., 2000; Shin et al., 2016). It is often associated with photodamage to skin and perilesional hyperpigmentation following high dose of irradiation. Moreover, the continuous long-term UV irradiation may induce a limited response of EL treatment. Indeed, one study observed the plateau of repigmentation between 20th and 30th treatment of EL (Choi et al., 2004). The exhaustion of the melanocyte reservoir was suggested to be a factor contributing to a limited response of continuous long-term UV treatment. The *in vitro* data also supported the role of cell exhaustion in which human melanocytes have a refractory period of tyrosinae activation during continuous UVB irradiation (Aberdam et al., 1993).

All these findings suggest that having regular intermission during EL treatment is physiologically more favorable than continuous treatment and it can also minimize photoadaptive response of the skin. We therefore investigated the efficacy of the cyclic on-off EL treatment compared to the conventional continuous EL treatment.

MATERIALS AND METHODS

A. Study design and population

A randomized, controlled, split-body, non-inferiority trial was designed. After obtaining informed consent, 12 patients with stable symmetric vitiligo less than 5 years' disease duration were enrolled. The patients taking systemic steroids or having enlarging lesions were excluded. The paired symmetric vitiliginous lesions were randomized to either the continuous or the cyclic on-off EL treatment. Total duration of study was 9 months. In cyclic on-off treatment, the cycle was arbitrarily determined that one cycle consists of a 2-month treatment period (on) and a consecutive 1-month intermission period (off) (total 3 cycles during the trial). This study was approved by the institutional review board of Ajou university hospital (AJIRB-MED-DE3-15-151) and St. Vincent's hospital (VC15DIMI0106).

B. Treatment protocol

The lesions were treated twice a week. Initial irradiation dose was 50 mJ/cm2 on face and 100 mJ/cm2 on trunk and extremities. If there had not been minimal asymptomatic erythema, energy level was escalated by 50 mJ/cm2. In cyclic treatment, the treatment resumed after intermission with the previously used irradiation dose. Topical tacrolimus 0.1% ointment was applied in both twice daily throughout whole length of the trial.

C. Assessment and primary outcome

Photographic documentation of lesions was conducted every month and the degree of repigmentation was assessed with a repigmentation rate (%) from the baseline by using an image analysis program (Digital Researcher for Vitiligo Area Evaluation, Dr. VAE, Korea).

An intention-to-treat analysis was planned, and last observation carried forward method was applied to impute the missing value in the presence of dropouts. The primary outcome was mean difference of quantitative changes in repigmented area

between continuous and cyclic on-off treatment. The non-inferiority margin was set at 10%. During intermission period in the cyclic treatment, the clinical changes such as loss of repigmentation or worsening of the vitiligo lesions were assessed.

D. Statistical analysis

All statistical analyses were conducted using R 3.2.4 (R Foundation for Statistical Computing, Austria) and a P value <0.05 was considered statistically significant.

RESULTS

A. Patient characteristics

Total 12 patients (9 females and 3 males) were enrolled. The median age was 54.5-year-old (range 14-72) and the median disease duration was 17 months (range 1-58). The total number of paired vitiliginous lesions was 32 (16 pairs) and those were most frequently located on face (43.75%), followed by trunk (18.75%) and extremities (37.5%).

B. Repigmentation rate of continuous and cyclic on-off excimer laser treatments

Overall 10 patients completed the trial. Two patients dropped out of the trial for personal reasons after 4 months and 7 months of treatment, respectively. The repigmentation rates were 51.4 ±35.2% in the continuous group and 49.2±34.7% in the cyclic group. The mean difference between the two groups was 2.194% (95% confidence interval: -4.982 to 9.370%), which was lower than the non-inferiority margin (Figure 1A-D, Table 1). Four cases (25%) showed better repigmentation of the cyclic treatment than the continuous protocol. The cyclic group did not experience a loss of repigmentation or worsening of vitiligo lesions during off period. Instead, continuous repigmentation was observed in 8 cases (50%) and fading of hyperpigmented areas during the intermission resulted in a more cosmetically acceptable repigmentation (Figure 1E-F). The mean number of treatments was 58 for the continuous treatment and 39.5 for the cyclic treatment. The mean total cumulative dosage was 25,800 mJ/cm^2 for those in the continuous group and 15,012 mJ/cm^2 for the cyclic group. There were no complications associated with the treatment during the study period.

Fig. 1. Repigmentation of vitiligo after continuous and cyclic excimer laser treatments. Patient 2 had vitiligo on perioral area before treatment (A) and showed repigmentation rates of 93.2% with a continuous treatment (number 1) and 95.5% with a cyclic treatment (number 2) at the end of the trial (B). Patient 4 had lesions on both iliac areas (C) and showed repigmentation rates of 58.9% with a continuous treatment (number 1) and 52.5% with a cyclic treatment (numbered 2) (D). (E, F) Continous repigmentation was observed during the 1-month intermission period (patient 9).

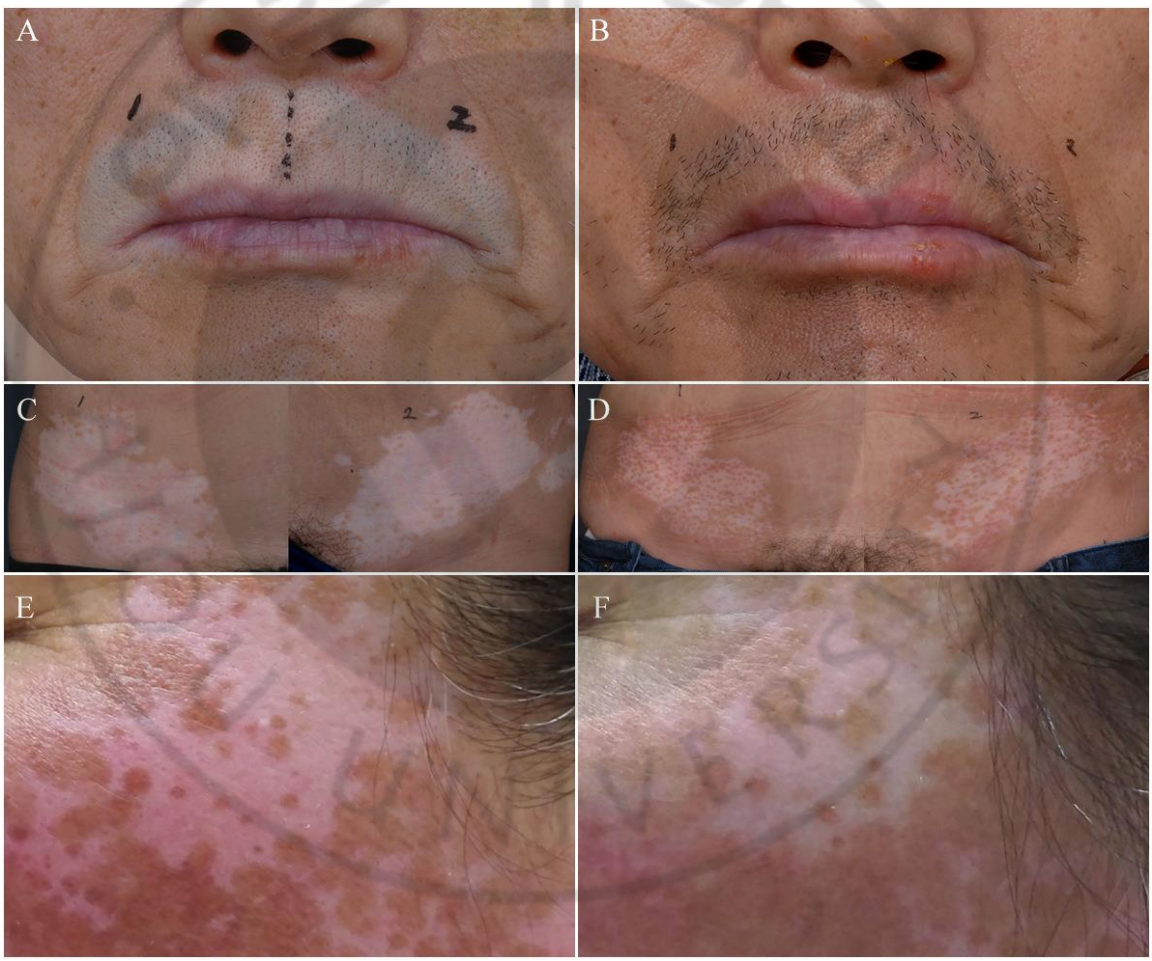

Table 1. Profiles and Repigmentation Rates From the Continuous and Cyclic On-Off Excimer Laser Treatments

Patient No.	Sex/Age	Lesion Site	Disease Duration (Months)	Repigmentation Rate (%)		
				Continuous (A)	Cyclic(B)	A - B
1	F/72	Face (cheek)	28	76.2	78.4	-2.2
2	M/71	Face (perioral)	57	93.2	95.5	-2.3
		Extremities (thigh)	57	18.7	6.1	12.6
3	F/43	Extremities (thigh)	6	25.5	68.4	-42.9
4	F/44	Trunk (abdomen)	58	58.9	52.5	6.4
5	M/14	Extremities (thigh)	40	85.3	74	11.3
6	F/56	Face (cheek)	3	92.9	90.6	2.3
		Extremities (hand)	3	85.1	64.1	21
7	M/70	Face (forehead)	13	16.5	12	4.5
		Extremities (hand)	13	65.2	59.6	5.6
8	F/70	Face (forehead)	24	20.6	14.2	6.4
		Face (cheek)	24	2.6	1.1	1.5
9	F/54	Face (cheek)	14	86.4	78.6	7.8
10	F/54	Trunk (abdomen)	5	78.7[a]	77.9[a]	0.8
11	F/49	Trunk (back)	20	7.2	8.7	-1.5
12	F/55	Extremities (thigh)	1	9.5[b]	5.7[b]	3.8
		Mean (SD)		51.4 (35.2)	49.2 (34.7)	2.19 (95% CI, -4.982–9.370)

Abbreviations: CI, confidence interval; SD, standard deviation.

[a] Repigmentation rate was assessed at 4 months due to withdrawal

[b] Repigmentation rate was assessed at 7 months due to withdrawal

C. Clinical changes during intermission period in cyclic on-off protocol

The cyclic group did not experience a loss of repigmentation or worsening of vitiligo lesions during off period. Instead, continuous repigmentation was observed in 8 cases (50%) and fading of hyperpigmented areas during the intermission resulted in a more cosmetically acceptable repigmentation (Figure 1E-F).

DISCUSSION

In the present study, the result of cyclic on-off EL treatment was non-inferior to those of conventional continuous treatment in vitiligo. The cyclic treatment could be associated with improved patient compliance because of less number of treatment sessions and less cumulative UV dose comparing the continuous treatment. The intermission would minimize photoadaptive response of the skin and also may reduce economic and time burdens of patients.

In our hypothesis, the exhausted melanocyte activity during continuous treatment may cause less therapeutic efficacy and the cell restoration during intermission may induce better repigmentation. However, we could not prove the superior efficacy of cyclic treatment in this study.

Nevertheless, 4 (25%) cases showed higher repigmentation rate of cyclic on-off protocol than continuous one, suggesting not only the topical tacrolimus but also other factors could have affected repigmentation in cyclic on-off protocol.

The continuous long-term UV irradiation may induce a limited response of EL treatment. Indeed, one study observed the plateau of repigmentation between 20th and 30th treatment of EL (Choi et al., 2004). The exhaustion of the melanocyte reservoir was suggested to be a factor contributing to a limited response of continuous long-term UV treatment (Shin et al., 2016). The in vitro data also supported the role of cell exhaustion in which human melanocytes have a refractory period of tyrosinae activation during continuous UVB irradiation (Aberdam et al., 1993). All these findings suggest that having regular intermission during EL treatment is physiologically more favorable than continuous treatment and it can minimize photoadaptive response of the skin.

Another interesting finding is that neither loss of repigmentation nor worsening of vitiligo lesions was observed during intermission. Instead, more homogenous pigmentation was observed after having intermission. The scattered pigmented spots

merged each other which suggest continuous repigmentation is occurring even during intermission. In addition, fading of the over-pigmented area during the break may contribute to more natural and cosmetically acceptable repigmentation color.

The present study had some limitation. First, the concurrent use of topical tacrolimus could attribute to our results (Kang et al., 2006; Passeron et al., 2004; Cavalié et al., 2015). Second, the sample population was small. Furthermore, the patient satisfaction has not been investigated in this study. Measuring the patient satisfaction could give us important information about the compliance.

CONCLUSION

The present study showed that cyclic EL treatment is as effective as conventional continuous treatment in vitiligo. The cyclic on-off treatment protocol could be promising in EL treatment for vitiligo, considering more homogeneity in repigmentation and lower cumulative dose. More controlled trials with large number of patients are needed to confirm our results.

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