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Original Article

Intense pulsed light combined with alpha-hydroxy acid peels in treatment of chloasma

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Abstract: Objective: To investigate the effect of intense pulsed light (IPL) plus alpha-hydroxy acid peels in patients with chloasma. Methods: Sixty chloasma patients were enrolled from Department of Dermatology in No.1 Hospital, Anhui Medical University between January 2015 and December 2017. The included patients were randomly divided into two groups, namely the test group and the control group. Patients in the test group underwent alpha-hydroxy acid peels and IPL, while those in the control group were given alpha-hydroxy acid peels alone. The treatment period was 8 weeks in both groups, with 30 patients in each group. The curative effect, overall skin lesion scores, patient satisfaction, adverse reactions, and serum superoxide dismutase (SOD) and malondialdehyde (MDA) expression were compared between the two groups. Results: The test group had an overall response rate of 86.7%, which was significantly higher than that (60%) in the control group, and the difference was statistically significant (P=0.017). The scores of patient satisfaction in the test group was significantly higher than that in the control group (3.2±0.7 vs. 2.4±0.5, P<0.001). The two groups had significantly lower overall skin lesion scores, higher SOD levels, but lower MDA levels after treatment than before treatment (all P<0.05). After treatment, patients in the test group showed significantly lower overall skin lesion scores (P<0.001), higher SOD levels (P<0.001), and lower MDA levels (P=0.001) than those in the control group. Differences in the incidence of adverse reactions were not significant different between the two groups (P=0.639). Conclusion: IPL combined with alpha-hydroxy acid peels exhibits obvious anti-oxidation effect. It can effectively cure chloasma and induce few adverse reactions, thereby leading to wide clinical application.

Keywords: Chloasma, alpha-hydroxy acid, intense pulsed light, curative effect

Introduction

Chloasma is a refractory pigmented disorder in the facial skin, in which the dynamic homeostasis between oxidation and anti-oxidation *in vivo* is destroyed, leading to the accumulation of lipid peroxide *in vivo* [1, 2]. Its degradation product malondialdehyde (MDA) may cause cross-linking of protein molecules to form pigment [3]. Superoxide dismutase (SOD), an antioxidant enzyme, can effectively scavenge oxygen free radicals and inhibit tyrosinase activity, thus preventing the occurrence of pigmentation [4]. MDA levels in patients with chloasma have been reported reported to be obviously higher than those in healthy controls, but SOD levels are significantly lower [5, 6]. However, the underlying etiology and pathogenesis of chloasma still remain unclear, and there is no ideal treatment at present [7].

Alpha-hydroxy acid is commonly used for clinical treatment of chloasma by affecting the activities of related epidermal enzymes such as sulfotransferase and phosphotransferase, lowering the epidermal electronegativity and adherence of keratinocytes, renewing the epidermis, and detaching the pigmented corneum [8].

Table 1. Criteria for treatment effects

Visual disappeared area	Color of skin lesions	Index decrease after treatment	Clinical response
>90%	Basically disappeared	≥0.8	Basically cured
>60%	Obviously lighter	≥0.5	Extremely effective
>30%	Lighter	≥0.3	Improved
<30%	Unapparent	<0.3	Ineffective

Table 2. Criteria for scoring skin lesion area and colors

Skin lesion area	Skin lesion color	Score
No lesion	Normal skin color	0
<2 cm^2 lesion	Light brown	1
2-4 cm^2 lesion	Brown	2
>4 cm^2 lesion	Dark brown	3

Nevertheless, chloasma is prone to recurrence and side effects after monotherapy, so a combined treatment is predominant in clinical practice [9]. Due to convenient operation, rapid onset of action and fewer complications, laser therapy has been gradually accepted by clinicians and patients for treatment of various pigmentary diseases [10]. Newly-developed intense pulsed light (IPL) can significantly improve the therapeutic effect of chloasma and relieve patient's pain based on the principle of selective photothermolysis [11]. However, there is no available report regarding the efficacy of newly-developed IPL combined with alpha-hydroxy acid peels in treatment of chloasma. Therefore, this study enrolled 60 chloasma patients from Department of Dermatology in No.1 Hospital, Anhui Medical University from January 2015 to December 2017 to investigate the efficacy of newly-developed IPL combined with alpha-hydroxy acid peels in treatment of chloasma, with the expectation to provide data support for clinical treatment of chloasma.

Materials and methods

Subjects

Sixty female patients diagnosed with chloasma in No.1 Hospital, Anhui Medical University from January 2015 to December 2017 were included in this study and they were randomized into the test group and the control group. Patients in the test group received alpha-hydroxy acid peels and IPL, whereas those in the control group were given alpha-hydroxy acid peels alone. There were 30 patients in each group. Inclusion criteria: female patients who met the diagnostic criteria for chloasma; patients with no dermatitis, dermatoma, photosensitivity or other diseases; patients without other laser treatment within 6 months before treatment or no use of hydroquinones and tretinoin within 3 months before treatment; patients with Fitzpatrick skin phototypes (FST) III to IV [12]. Exclusion criteria: (1) patients predicted to be unable to actively cooperate with the study postoperatively, such as avoiding light and applying sunscreen; (2) patients with severe liver and kidney dysfunction, cardio and cerebrovascular diseases, photodermatoses, and underlying diseases such as infectious disease, diabetes or hematopoietic disease; (3) pregnant or lactating women; (4) patients allergic or intolerant to alpha-hydroxy acid. This study was approved by the Ethics Committee of No.1 Hospital, Anhui Medical University and obtained all the patients' informed consent.

Methods

IPL treatment: Before treatment, the affected skin was cleaned and coated with cool gel at 4°C. According to the location and color of skin lesions, as well as FST classification, the parameters of pulsed light were defined as follows: energy intensity 13-18 J/cm^2; filter 560 nm, 590 nm, and 615 nm; pulse time 3-4 ms at an interval of 25-40 ms. Skin was given cold compress for 1-3 seconds and cooled with ice-packs for 10-30 minutes before and after IPL treatment. Patients were advised to avoid light and apply sunscreen during the treatment intervals and at 4 weeks after treatment. Each patient received four treatments at two-week intervals.

Alpha-hydroxy acid peels: Patients were placed in a supine position to clean their facial skin. Alpha-hydroxy acid at an initial concentration of 20% was applied to the patient's face, avoiding the eyes and mouth, maintaining for 2-5 minutes. When the patients were present with erythema, psoriatic lesions or any discomfort, the skin was neutralized with neutralizing solution

Table 3. Comparison of general information between two groups

Group	Case (n)	Age (year)	Course of disease (year)	Type of skin lesions			
				Upper face	Butterfly-shaped	Generalized	Lower face
Test group	30	35.7±2.8	4.1±0.8	8	7	10	5
Control group	30	35.1±2.6	3.8±0.6	9	5	12	4
t/χ^2		0.860	1.643		0.687		
P		0.393	0.106		0.876		

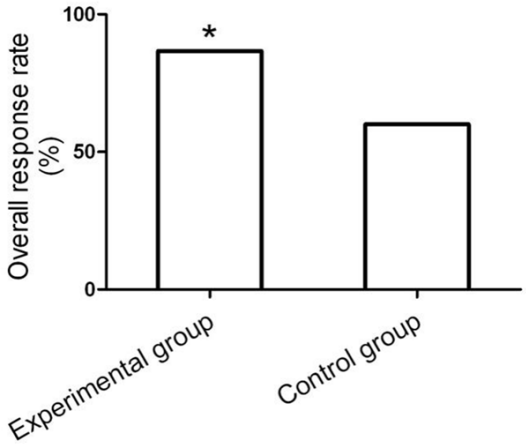

Figure 1. Overall response rates for the two groups. *P<0.05, compared with the control group.

and cold compress for 10 minutes, followed by external use of Winona Anti-Sensitive Moisturising & Smoothing Mask for 3 days. Alpha-hydroxy acid peels were given once every 2 weeks, with total 4 times as a course, requiring sunscreen protection during treatment.

As for the combined therapy, IPL was performed at 1 week after alpha-hydroxy acid peels, with the same method as described above, for 4 times in total. The treatment period was 8 weeks.

Outcome measures

The curative effects were compared between the two groups. The criteria for clinical response evaluation are shown in **Table 1** [13]. The overall response rate was calculated as (Cases of basically cured + extremely effective + improved)/total number of cases * 100%.

The overall skin lesion scores between the two groups were compared. The overall skin lesion scores were the sum of skin lesion area scores and skin lesion color scores, and the scoring criteria are shown in **Table 2**.

Patient satisfaction was compared between the two groups. At the completion of the treatment, all patients were scored according to the patient's satisfaction checklist, and then they made a subjective assessment of the curative effects: high satisfaction and extreme effectiveness as 4 points, obvious improvement as 3 points, slight changes as 2 points, no changes as 1 point, and deterioration as 0 point.

Adverse reactions were compared between the two groups, including local irritation, allergy symptoms, and systematic symptoms.

Serum SOD and MDA levels were compared between the two groups. Before and after treatment, overall SOD activity in serum was tested by the xanthine oxidase method at colorimetric wavelength of 550 nm, and the SOD activity was expressed as U/mL. MDA level was detected by the thiobarbituric acid method at colorimetric wavelength of 532 nm, and the MDA content was expressed as nmol/mL.

Statistical analysis

All data were analyzed using the SPSS statistical software, version 19.0. Enumeration data were expressed as rates and compared by the chi-square test. Measurement data were described as mean ± standard deviation and compared by the independent sample t-test between two groups. Paired t-test was applied for intra-group comparison before and after treatment. Differences were considered statistically different where P<0.05.

Results

Comparison of general information between two groups

The two groups were insignificantly different in age, course of disease and types of skin lesions (**Table 3**).

Table 4. Comparison of overall skin lesion scores between two groups

Group	Case (n)	Total scores of skin lesions		t	P
		Before treatment	After treatment		
Test group	30	3.7±0.9	2.2±0.4	9.875	<0.001
Control group	30	3.6±0.8	2.7±0.6	8.367	<0.001
t		0.651	3.798		
P		0.455	<0.001		

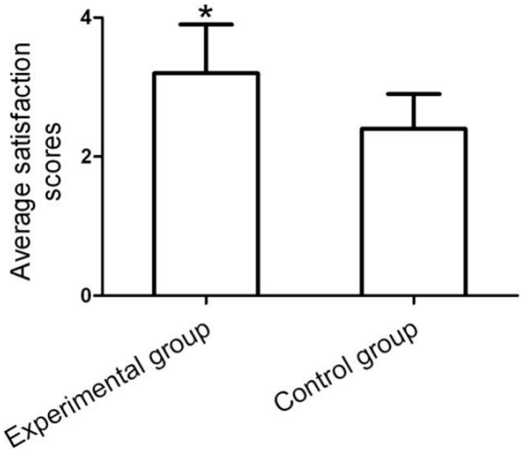

Figure 2. Patient satisfaction scores for the two groups. *P<0.05, compared with the control group.

Comparison of overall response rate between two groups

In the test group, 7 cases were basically cured; 13 cases showed extremely effective; 6 cases improved and 4 cases were ineffective, with an overall response rate of 86.7%. In the control group, 2 basically cured cases, 12 extremely effective cases, 4 improved cases and 12 ineffective cases contributed to the overall response rate of 60%. The overall response rate of the test group was significantly higher than that in the control group (χ^2=5.649, P=0.017; **Figure 1**).

Comparison of overall skin lesion scores between two groups

No significant difference was noted in total scores of skin lesions before treatment between the two groups. After treatment, the overall skin lesion scores of both groups were significantly decreased (P<0.05). The overall skin lesion scores in the test group were lower than that in the control group, with statistically significant difference (P<0.05; **Table 4**).

Comparison of patient satisfaction scores between two groups

The patient satisfaction score was 2.4±0.5 in the control group and 3.2±0.7 in the test group, and there were statistically significant differences between the two groups (t=5.094, P<0.001; **Figure 2**).

Comparison of adverse reactions between two groups

In the test group, skin irritation was reported in one patient and gastrointestinal reactions in two patients during the treatment. In the control group, pruritus was present in one patient, and desquamation in one patient during the treatment. The difference in the incidence of adverse reactions between the two groups was not statistically significant (χ^2=0.220, P=0.639). All adverse reactions of the two groups resolved after symptomatic treatment.

Comparison of serum SOD and MDA expression levels between two groups

There was no significant difference in the levels of SOD and MDA before treatment between the two groups. After treatment, the SOD levels were significantly elevated but the MDA levels were significantly decreased in the two groups; the difference was statistically significant (P<0.05). The SOD level was significantly higher (P<0.001), but the MDA level was significantly lower (P=0.001) in the test group than in the control group; the difference was statistically significant (**Table 5**).

Discussion

Chloasma, also known as malar rash, is one of the clinically common skin diseases. This disease develops slowly, lasts for a long course, and can be aggravated after sun exposure. It is more predominant in middle-aged and young people. The male-to-female ratio of patients with chloasma is approximately 1:9. Chloasma may affect the appearance of patients to varying degrees, and has negative impacts on personal life, social activities and psychology of

Table 5. Comparison of serum SOD and MDA levels between two groups

Group	Case (n)	SOD		t	P	MDA		t	P
		Before treatment	After treatment			Before treatment	After treatment		
Test group	30	67.4±4.1	98.2±4.8	24.721	<0.001	4.7±0.6	3.8±0.4	17.863	<0.001
Control group	30	68.1±4.4	84.6±4.7	19.867	<0.001	4.9±0.8	4.2±0.5	16.708	<0.001
t		0.638	11.090			1.095	3.422		
P		0.526	<0.001			0.278	0.001		

patients. In recent years, due to lifestyle, work pressure, and abuse of cosmetic products, the incidence of chloasma has significantly increased and there is a trend of patients with younger age. At present, pathogenesis of chloasma remains unclear. Studies have shown that chloasma can occur on any type of skin and has a detrimental effect on the human skin barrier [14, 15].

Clinically, chloasma is treated with oral drugs, laser, and chemical peeling, but their efficacy varies. Ideal treatment methods are currently unavailable. Due to the complex etiology of chloasma, an increasing number of scholars choose a combined therapy. IPL used in this study is the fifth-generation photon technology launched in 2011. IPL treatment of pigmentary lesions is based on the principle of selective photothermolysis, in which light is selectively absorbed by melanocytes and melanosomes in skin. Under the premise of not damaging the skin, the targeted therapeutic effect can be achieved when the pulse time is less than or equal to the thermal relaxation time of the target (melanin particles), and energy intensity is sufficient to destroy and decompose the target [16]. Studies have shown that the fifth generation of new photons can eliminate the traditional IPL energy spikes, apply uniform intensity to targets, relieve pain in chloasma patients during treatment, and improve safety of patients [17]. Alpha-hydroxy acid used in this study is directly extracted from fruits, with a small molecular weight, good water solubility, strong skin affinity, and high safety. Previous studies have demonstrated acceptable effect of alpha-hydroxy acid in treatment of chloasma [18]. Its mechanisms of action include regulation of abnormal hyperkeratosis, acceleration of metabolism and decomposition of melanin, as well as improvement of skin texture including shrinking pores and removing fine wrinkles. Other studies indicate that higher concentration of alpha-hydroxy acid is associated with better effect in the treatment of chloasma, but also adds the risks of pigmentation [19]. Although laser therapy is regarded as a safe option, there are still risks of long-term pigmentation and recurrence after treatment [20]. Polnikorn et al. argued that Q-switched laser at 1064 nm and alpha-hydroxy acid can reduce the recurrence rate of refractory chloasma. Therefore, the combined therapy is conducive to the chloasma treatment [21].

In this study, the combined therapy of IPL and alpha-hydroxy acid peels was used to treat chloasma. The results showed that IPL combined with alpha-hydroxy acid peels resulted in a higher overall response rate, a lower total score of skin lesions and higher patient satisfaction than alpha-hydroxy acid peels alone, and the difference was statistically significant between the two groups. Additionally, the combined therapy did not increase the risks of adverse reactions, which is basically consistent with the finding reported by Cho et al. [22]. Abnormal oxidative stress plays an important role in the development of chloasma. The declined scavenging capacity of free radicals leads to severe collagen destruction and abnormal production, as well as decreases in skin tissue viability and elasticity [23]. This study showed that after combined therapy, SOD levels were significantly higher, but MDA levels were significantly lower than with alpha-hydroxy acid alone, suggesting that combined therapy can better improve oxidative stress in patients with chloasma. This result is consistent with that of Park et al. [24].

In summary, IPL combined with alpha-hydroxy acid peels led to better efficacy, more effective regulation of oxidative stress, higher patient satisfaction and fewer adverse reactions. It is a safe and feasible treatment method. However, the present study failed to follow up

patients with chloasma for long-term outcomes, and the mechanism of the combined therapy is not yet clear. Therefore, further studies are needed to improve the efficacy of patients.

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Disclosure of conflict of interest

None.

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