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·Laser Photonic Technology·

A study to evaluate the efficacy of clearance of melasma with a 1550-nm fractional laser versus a ruby laser

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[Abstract] Objective To assess the efficacy and safety of clearance of melasma with a 1550-nm non-ablative fractional laser, and made a comparison to the Q-switched ruby laser. **Methods** 20 Chinese female patients with melasma on both sides of face symmetrically were recruited. Choosing fractional side and ruby side according to the randomization table. Fractional side had 5 times of 1550-nm fractional laser sessions and ruby side had 10 times of 694-nm fractional laser sessions. Evaluation criterias included evaluating of melasma area and severity index(MASI), confocal laser scanning microscopy(CLSM), ect. Side-effects were also recorded. **Results** Compared to baseline, the MASI scores of both sides showed an obvious decline after four times of sessions. The score of ruby side reduced more quickly than the fractional side at the beginning, but it increased and exceeded the score of fractional side three months after the final treatment. The CLSM images showed a drastic decreasing of melanin granules in the basal layer of epidermis one month after the final treatment. For the ruby side, there were also three cases of hyperpigmentation. **Conclusion** In a short period of time, the ruby laser showed a drastic improve on the melasma, but the fractional laser had lower recurrence rate and less side effects.

[Key words] Melasma; Laser therapy; Fractional photothermolysis

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Melasma is a common chronic disorder of skin pigment metabolism which has complex etiology and is difficult for treatment. In recent years, different lasers have been attempted in treating melasma and have achieved good results. Fractional laser can be divided into ablative laser and non-ablative laser according to whether it can cause exfoliation of dermis and epidermis. 1550nm fractional laser is a kind of non-ablative fractional laser. At present, medical workers do just little research on the treatment of pigmented diseases. This study aims at exploring the effect and safety of laser in the treatment of melasma, and a comparison is made between 1550nm fractional laser and ruby fractional laser. At the same time, confocal laser scanning microscopy (CLSM) is applied to further explore the effects on melanocytes and melanin granules.

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1 Materials and Methods

1.1 Diagnosis criteria

① Clearly-defined light brown to dark brown patches on the face, usually distributed symmetrically, and no inflammation and scale; ② No obvious conscious symptoms; ③ Female

multiplex, mainly occurs after puberty; ④The disease may be seasonal, often severe in summer and mild in winter; ⑤Pigmentation caused by other diseases is excluded.

1.2 Criteria for elimination

①Patients with facial skin lesions, deformities and serious diseases; ② Patients with scar constitution, immune deficiency and pigmentation history; ③ Patients who have recently taken photosensitive drugs or cannot avoid postoperative light and are under skin care; ④Patients with severe endocrine, cardiovascular and diseases of other systems; ⑤Patients who have used any drugs that can change skin color within 6 weeks; ⑥ Patients with unrealistic expectations.

1.3 Objects of study

Twenty female patients with melasma were treated in our outpatient department from November 2013 to May 2015. Their age ranges from 26 to 53 years old, with an average age of 38.36 years old. The duration of their illness ranges from 0.5 to 16 years, with an average of 8.41 years. Among them, there were 11 cases on zygomatic cheeks, 4 cases on frontal and 5 cases of generalized type. Skin type: type III in 9 cases and type IV in 11 cases. Judge by using wood's lamp, there were 8 cases of epidermal type and 12 cases of mixed type. No external medicine, laser or systemic therapy was taken or used within 6 weeks. All patients participated in the clinical test and signed the informed consent and photo use agreement on a voluntary basis.

1.4 Methods of study

1.4.1 Treatment equipment and parameters

Parameters of 1550nm non-ablative fractional laser (GSD, Shenzhen, China): Spot diameter is 15mm, single spot energy is 30-40mJ, scanning density is 100-200dots/cm^2, overlapping is 10% - 20%, and scanning is for 2-3 times; Parameters of Q-switched ruby fractional laser (Asclepion, Germany): spot diameter is 7mm, energy density is 2.5-3J/cm^2, it is non-overlapping, and scanning is for 1 time. The parameters of the first treatment were set according to the skin color, age, activity of the disease and the reaction of the lesions at the laser irradiation part, and the objective of the treatment should be slightly red at lesion part of the skin. Each treatment parameter was adjusted according to the last efficacy, adverse reactions and patients' self-evaluation.

1.4.2 Therapeutic methods

The fractional side and ruby side were selected according to the random number table method. The basic situation of patients was learned and recorded in details. Before treatment, the patient's face was cleaned, each of their personal files was established, and digital camera was used to take their photos, and they were placed on file. 1550nm fractional laser treatment was performed for 5 times on the fractional side with an interval of 1 month, and ruby laser treatment was performed for 10 times of on the ruby side with an interval of 2 weeks. Anesthesia was not used in the whole process, and cold compress was applied for 30 minutes after operation. Sun exposure was avoided during the whole period of clinical study, and sunscreen (SPF $\geq$ 30) must be used. Use of skin bleach and tretinoin drug was forbidden during the treatment.

1.5 Efficacy evaluation standard

1.5.1 The MASI (melasma area and severity index) score [2,3] was assessed by two experienced dermatologists before the first treatment, and the 3rd, 5th, 7th and 9th treatment, and 1 and 3 months after the last treatment. The score of MASI was = 0.3 (DF + HF) AF + 0.3 (DMR + HMR) AMR + 0.3 (DML + HML) AML + 0.1 (DC + HC) AC; A= the area of melasma, D= the degree of macular deepening, H = the degree of pigment uniformity, F= forehead, MR = right cheek, ML = left cheek, C = chin; A is rated as 6 levels, 0 is no skin lesion, 6 is that the area of melasma accounts for 90% -100%; D is rated as 4 levels: 0 is no deepening, 4 is severe deepening; H is rated as 4 levels: 0 is extremely inconsistent, 4 is almost consistent;

score improvement rate = (total score of MASI before treatment - total score of MASI after treatment /total score of MASI before treatment ×100%). The higher the score, the more serious the lesion is.

1.5.2 Pathological stereological examination and adverse reaction record

CLSM was used to detect the lesions before the first treatment, immediately after treatment, 1 month and 3 months after the last treatment respectively. The test location is the most serious skin lesions on both sides of the face. Before the first test, the location shall be marked and photos taken with the camera to record the test location and ensure the accuracy of the test. In addition, the recurrence and adverse reactions shall be recorded.

1.6 Statistical methods

SPSS20.0 statistical software was used to analyze, T-test was conducted for the measurement data, and analysis of variance was employed for comparison between groups. The test level of $\alpha = 0.05$.

2 Results

2.1 Clinical efficacy

All 20 patients completed the treatment. The mean value of both sides' overall MASI scores decreased significantly before the fifth treatment compared with that before the first treatment, and the results were statistically significant ($P < 0.05$). The overall MASI score of ruby side decreased faster than that of fractional side, but increased more than that of fractional side 3 months after the last treatment. The score of mixed type on fractional side significantly decreased than that of epidermis type, while that of epidermis type on Ruby side significantly decreased than that of mixed type, and the difference is significant ($P < 0.05$), and the difference between the other types is not significant. 3 months after the last treatment, the difference of mean value of overall MASI score and the total improvement rate between the fractional side and ruby side ($P < 0.05$)t was statistically significant, and differences at other time points (as shown in Table 1 & 2, and Figure 1& 2) were not significant .

2.2 Pathological stereological examination

Before treatment, there was a lot of melanin in the basal layer of melasma patients, which were round or oval in shape and distributed in granules. Most of them gathered around the hair follicle, and there were many dendritic melanocytes. CLSM images at 30 min after ruby laser treatment showed that the melanin structure in the lesion area was incomplete to varying degrees, the cell contour was disintegrated and blurred, and the high refractive granular material was densely distributed. One month after the last treatment, the brightness, density and volume of melanin in the lesions on both sides of the patient reduced or decreased, and the shape of melanin gradually tended to be the same. Three months after the last treatment, the lesions on both sides recurred. It could be seen that the distribution density of melanin in the basal layer has been increased, the melanin increased, and the brightness enhanced (Fig. 3, as shown by the arrow).

Table 1 MASI Score and Improvement rate ($\bar{x} \pm s$, points) at Each Time Point before and after the Treatment of Fractional Side

Type		n	Before treatment	T×3	T×5	T×7	T×9	1 month later	3 months later	Improvement rate 1(%)	Improvement rate 2(%)
Fitzpatrick type	Type III	9	14.96±1.02	13.13±2.34	12.58±2.56	11.17±1.06*	9.69±0.95*	7.35±1.33*	10.21±1.18*	50.8%	31.8%
	Type IV	11	14.99±2.13	13.35±1.62	12.51±1.16*	10.83±2.31*	9.35±1.27*	7.11±1.09*	10.07±1.20*	52.5%	32.8%
Histological type	Epidemal type	8	14.86±1.67	13.46±1.25	12.77±2.10	11.25±2.85*	10.34±1.67*	8.63±0.36*	10.96±2.38*	41.9%	26.2%
	Mixed type	12	14.92±1.79	13.58±3.10	11.83±1.59*	10.68±2.46*	8.92±0.66*	6.35±1.27*	9.34±1.53*	57.4%	37.3%
Overall		20	14.93±1.65	13.38±2.07	12.42±1.85*	10.98±2.17*	9.58±1.13*	7.36±1.01*	10.15±1.57*	50.7%	32.0%

Note: T×3 in the table indicates the improvement rate before the third treatment, and so on; improvement rate 1 (%) indicates the improvement rate 1 month after the last treatment compared with that before treatment; improvement rate 2 (%) indicates the improvement rate 3 months after the last treatment compared with that before treatment; * indicates that the difference is statistically significant compared with that before treatment ($P < 0.05$).

Table 2 MASI Score and Improvement rate ($\bar{x} \pm s$, points) at Each Time Point before and after the Treatment of Ruby Side

Type		n	Before treatment	T×3	T×5	T×7	T×9	1 month later	3 months later	Improvement rate 1(%)	Improvement rate 2(%)
Fitzpatrick type	Type III	9	14.85±2.12	13. 31±1.94	12.15±3.16	11.02±2.16*	9.17±1.89*	7.25±2.48*	12.86±1.62	51.2%	13.4%
	Type IV	11	14.92±1.93	13.34±2.47	11.87±1.69*	10.57±1.45*	8.89±2.07*	6.93±2.11*	12.31±1.15*	53.6%	17.5%
Histological type	Epidemal type	8	14.88±2.21	13.33±2.19	11.29±1.41*	9.19±0.96*	8.08±3.10*	5.03±1.79*	11.84±1.88*	66.2%	20.4%
	Mixed type	12	14.89±0.91	13.45±2.77	12.24±1.08	11.51±1.23*	9.42±1.71*	7.71±0.19*	12.98±2.91	48.2%	12.8%
Overall		20	14.89±1.79	13.36±2.34	11.89±1.84*	10.57±1.45*	8.89±2.19*	6.73±1.64*	12.50±1.89	54.8%	16.1%

Note: T×3 in the table indicates the improvement rate before the third treatment, and so on; improvement rate 1 (%) indicates the improvement rate 1 month after the last treatment compared with that before treatment; improvement rate 2 (%) indicates the improvement rate 3 months after the last treatment compared with that before treatment; * indicates that the difference is statistically significant compared with that before treatment ($P < 0.05$).

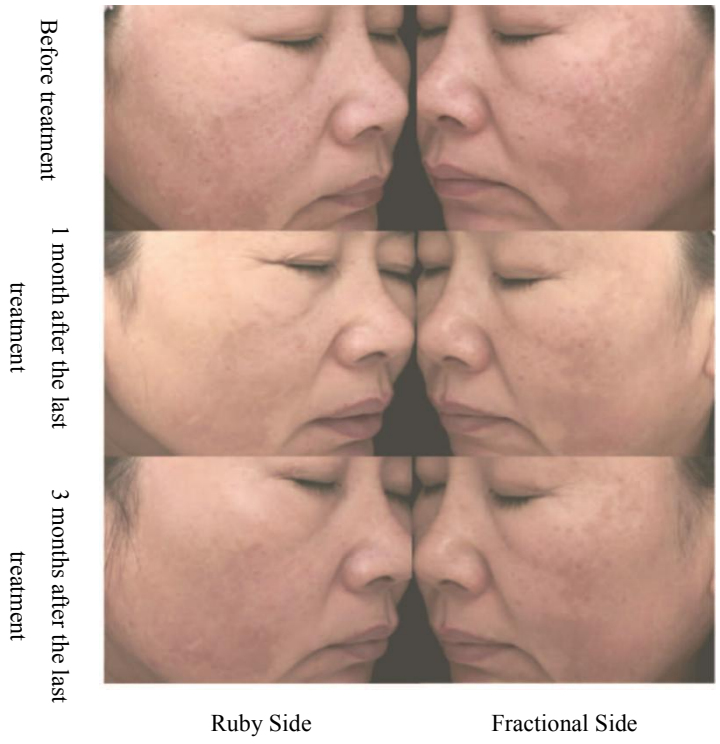


Fig.1 Clinical manifestation before and after laser treatment

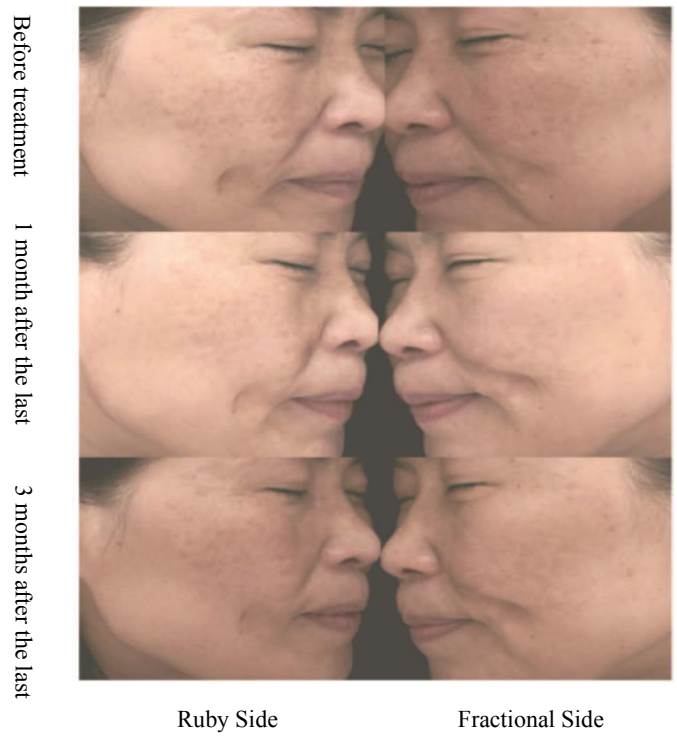
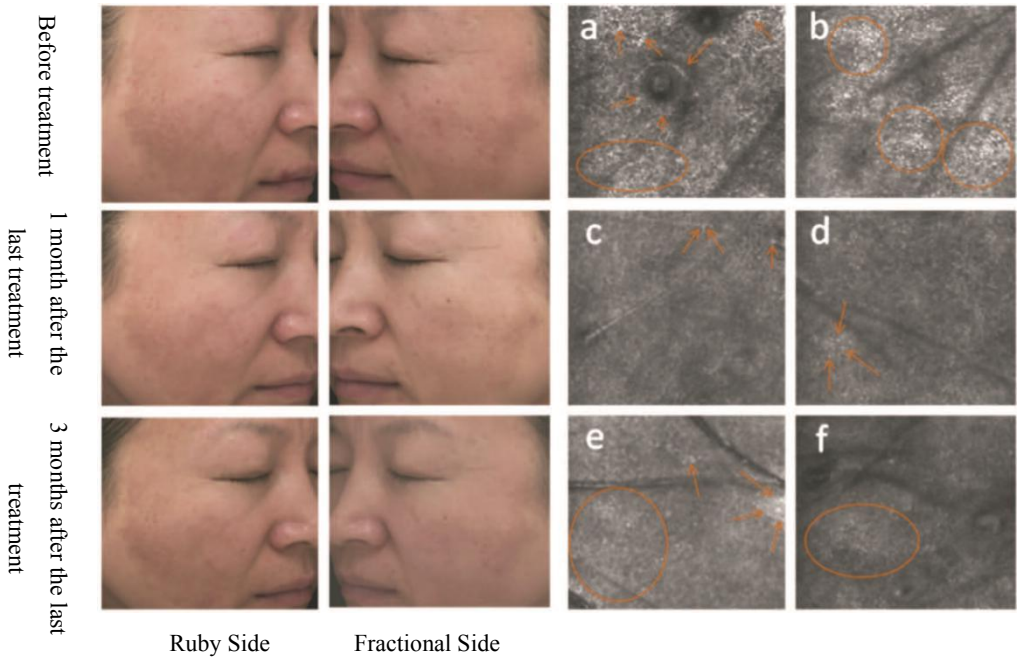


Fig.2 Clinical manifestation before and after laser treatment

2.3 Adverse effects

There was erythema, edema, scab and pain on both sides. The ruby side was more painful than the fractional side, and it was easier to scab. There was no hyperpigmentation on the fractional side, but 3 cases of hyperpigmentation on the ruby side. 3-5 days after treatment, both sides got melanized, and then the color spots gradually subsided (as shown in Table 3).



a is before treatment; b is immediately after the first treatment of ruby side; c, d is 1 month after the last treatment of ruby side and fractional side; e, f is 3 months after the last treatment of ruby side and fractional side

Fig. 3 Clinical manifestations and corresponding manifestation of CLSM skin basal layer before and after laser treatment

Table 3 Subjective Efficacy and Safety Score of Patients ($\bar{x}$, points)

Group	Adverse reaction							Degree of satisfaction	Degree of pain*
	Erythema	Edema	Blister	Scab*	Pigmentation	Hypopigmentation	Scar		
Fractional side	1.80	2.00	0.00	0.35	0.00	0.00	0.00	5.65	2.35
Ruby side	1.65	1.80	0.00	1.75	0.45	0.00	0.00	5.10	5.40

Note: the value is the mean value of individual score at each time point before and after treatment; * indicates that the difference in the mean value of scores on both sides is statistically significant ($P < 0.05$).

3 Discussions

With the proposal and application of selective photothermal effect, laser has become a safe and effective method for the treatment of pigmented diseases [4]. However, laser therapy is a double-edged sword, which brings benefits to patients, but also inevitably has some limitations. Therefore, it is urgent to develop new technologies, further raise the improvement rate of color spots, reduce the recurrence rate, and reduce adverse reactions [5].

The therapeutic mechanism of fractional laser is local photothermal effect, including ablative and non-ablative. 1550nm fractional laser is non-ablative fractional laser. The principle of this laser in treating melasma can be explained by "Shuttle Bus" function [6], that is, the target color base of 1550nm fractional laser is water without special absorption of pigment. However, due to the local photothermal effect, tissue apoptosis occurs in the path of local heating. In the process of apoptosis, many cytokines will be released, thus starting the repair and regeneration of the whole area of skin. In this process, the

excessive pigment mass will be metabolized, most of which will be metabolized along the lymphatic or blood circulation after phagocytosis of phagocytes, and then excreted out of the human body through exfoliation of epidermis. Although the curative effect of this treatment is stable and safe, it takes effect slowly.

Ruby fractional laser has been widely used in clinical treatment of pigmented diseases and has achieved good results. Its main treatment mechanism is the principle of light explosion. In the treatment of melasma, in order to avoid the use of excessive energy leading to macular recurrence, the application energy is generally small, which produces the "laser toning" effect [7]. That is: when the weak laser hits the skin, due to its lack of energy, it rarely produces blasting effect, but it can shorten the dendritic cells of melanocytes through the effect of light modulation, so even if melanocytes produce melanin, they cannot transmit it to keratinocytes through the dendritic cells, so it has therapeutic effect on pigmentation. This therapeutic method is quick and effective, but its limitation is that, first of all, it only inhibits the transmission of melanin from dendrites to keratinocytes, but melanin is still produced. If the treatment is stopped, the dendrites can still transmit melanin to keratinocytes, which will lead to the recurrence of color spots. Secondly, if the laser irradiation on the color spots is not uniform, pigmentation and hypopigmentation is prone to occur alternately.

We found through this study that ruby laser treatment of melasma has significant short-term effect, but the recurrence rate is high, and the adverse reactions are great, while 1550nm fractional laser has good stability and high safety, but the effect is slow. 1550nm fractional laser is more effective in the treatment of mixed lesions than lesions of epidermis, but ruby laser is the opposite. In our opinion, the reason may be that the short pulse of ruby laser has a certain blasting effect on epidermal melanin, but the short wavelength does not have enough penetrating power on the skin, while the longer wavelength of 1550nm fractional laser can penetrate the dermis and epidermis, but it does not focus on the effect on epidermal melanin. We also found through the study that the treatment effect of patients with dark skin is better, and we think that the reason is that patients with dark skin have dark melanin, which has stronger laser absorption ability.

In this study, we noticed that 3 cases of hyperpigmentation were caused by ruby fractional laser treatment, so the problem of serious adverse reactions is still difficult to tackle. In order to reduce the above situation as much as possible, the authors think that the energy density should be adjusted cautiously while using Ruby fractional laser to treat melasma, and the treatment should be started from the minimum energy, with the aim of treatment of face turning slightly red. The choice of patients should also be cautious, and ruby laser should not be used for patients with mixed type of dermis and epidermis, and those with severe color spots and active melanocytes. After laser treatment, be sure to pay attention to skin care, strengthen postoperative sun blocking, and we suggest that sun protection factor (SPF) $\geq$ 30.

The mechanism of the treatment of melasma with 1550nm fractional laser is still in the preliminary stage. In this study, CLSM was used to observe the lesions in the treatment area. The results were consistent with the clinical manifestations, but the real mystery of the treatment mechanism has yet to be revealed. Moreover, the follow-up time of this study is still short, and the number of samples is very limited. Therefore, it is necessary to further extend the follow-up time, increase the number of samples, and explore the therapeutic mechanism from the perspective of histopathology or gene level.

Due to the different mechanisms of different types of laser treatment of melasma, and the

significant difference in the efficacy of different types of melasma, even the skin color, age, gender, etiology, treatment methods used and other factors of patients will more or less affect the treatment, In the opinion of the authors, we should study the effect of different factors and different kinds of laser treatment and the choice of treatment parameters more carefully in order to further understand the laser indications and clinical application methods. For the treatment of melasma, it is recommended that we should combine different laser instruments, such as application of ruby laser treatment for 2-3 times to improve symptoms quickly, and then non-ablative fractional laser treatment to achieve the overall repair of the epidermis and metabolism of residual pigment mass [8]. This alternative therapy can solve the problems of slow onset time of non-ablative fractional laser therapy and high recurrence rate of ruby laser therapy, and achieve the effect of complementing each other.

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