Melasma Treatments: A Review of Laser Therapies and the Integration of Reflectance Confocal Microscopy

Reflectance confocal microscopy may play a role in melasma stratification and treatment assessment.

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The currently available laser melasma treatments have varying utility values. Finding the appropriate treatment should be based upon skin type, the type of melasma, previous response to other treatments, and scientific evidence. Using reflectance confocal microscopy for melasma class identification as well as for monitoring treatment can provide insight into the effectiveness of therapy.

Melasma is a dysfunction of the skin’s pigmentation factory. Melanin, produced by melanocytes, and stored in melanosomes, is the skin’s natural pigment. These melanin-laden cells contribute to the color of skin. Melanin synthesis starts with the conversion of L-tyrosine to L-dopa, which in turn is converted to L-dopa-quinone inside the melanosomes. The reaction is catalyzed by the enzyme tyrosinase, and a dysfunction of these biochemical reactions leads to melasma. The result is a light to grey-brown hypermelanosis of sun-exposed areas. It is most commonly observed among women with highest prevalence seen in Fitzpatrick skin types IV to VI. Among women, those of child-bearing age are at the highest risk; men, on the other hand, represent only 10 percent of those affected.

Histologically, melasma is divided into three types: epidermal, dermal, and mixed, demarcated by Wood’s lamp. There is increased melanin in the basal, suprabasal, and stratum corneum in epidermal melasma. In the dermal variety, the superficial and deep dermis are laden with melanophages in the perivascular array. The mixed type has pigment deposition in the epidermis and dermis.

New data now supports the use of reflectance confocal microscopy in the classification of melasma. Confocal microscopy quantifies the amount of pigment in each layer, classifying all melasma as the mixed type with either epidermal or dermal components predominating.

With this understanding, the need to treat melasma becomes imperative. While a plethora of inexpensive yet marginally efficacious topical applications is available, an analysis of laser treatments is necessary, given their significant cost and possible adverse outcomes. Our goal is to review current laser treatment modalities for melasma, focusing on long-term benefits and effects of these treatments. The use of confocal microscopy for diagnosis and stratification into melasma types as well as assessment of therapy will also be addressed for each modality reviewed.

METHODS

A literature review was conducted through PubMed and Ovid search engines. Search terms included “melasma,” “recalcitrant melasma,” and “melasma laser treatments.” Each treatment was also used as a search term along with “confocal microscopy” to find specific articles in which both are discussed.

RESULTS

Laser Treatments. Laser treatments have shown promise in the treatment of melasma, especially in darker-skinned patients. There are a number of laser modalities that can be used to treat melasma, including ablative and nonablative fractional lasers, Q-switch lasers, and Erbium:YAG lasers.

Ablative CO₂ Laser. The ablative carbon dioxide (CO₂) laser has many uses including treatment of the sequelae of photoaging. A short, high-energy burst of the 10,600nm CO₂ wavelength laser vaporizes intra- and extracellular water, causing tissue ablation. The short burst is targeted to limit...
Fractional photothermolysis (FP) combines the efficacy of ablative and the tolerability of non-ablative lasers to treat conditions like melasma. The device emits pixilated light to create three-dimensional zones of thermal damage or ‘microthermal zones’ (MTZs). The small zones of thermal damage allow for rapid epidermal repair, while resurfacing at the same time. It differs from ablative skin resurfacing in not producing a uniform patch of epidermal or dermal injury.22

Hantash and colleagues using a 1550nm single-mode fiber laser found that FP created MTZs with an intact stratum corneum. Within the epidermis there was vacuolar formation from extruded dermal material as the dermal-epidermal junction is weakened above the zones of coagulation. The epidermal debris incorporates dermal melanin, which is ‘shuttled’ out. This is then exfoliated along with the stratum corneum. This mechanism of shuttling of dermal content underlies the removal of dermal melanin.33

The dermal injury wrought by FP leads to the release of inflammatory mediators that remodel the dermal matrix through increased collagen synthesis and fibroblastic activity. Goldberg, et al. undertook a study to link the histologic and ultrastructural changes brought about by treatment with FP. They examined biopsy specimens from 10 subjects who had epidermal melasma. They had been treated with 1550nm erbium:glass laser (Fraxel SR 750, Solta Medical) every two weeks for four sessions. The specimens were taken post-treatment and three months after the last session. A relative decrease in melanocytes on histology compared to baseline was observed. Electron microscopy examination revealed fewer melanocytes and an absence of melanin in the surrounding keratinocytes compared to pre-treatment specimens. The results of the study correlated the clinical efficacy observed with the histological picture.34

Rokhsar, et al. conducted a study on 10 female patients with melasma who had not responded to previous interventions. They were treated at one- to two-week intervals with the Fraxel laser (Solta Medical). Between four and six treatment sessions were given. Physician evaluation determined that 60 percent of patients achieved 75 to 100 percent clearing and 30 percent had less than 25 percent improvement. The patients had similar assessments except for one patient, who graded herself as 50 to 75 percent improved as opposed to the physician grading of greater than 75 percent.35

A clinical study was conducted by Lee, et al. on 25 patients who received four monthly FP sessions and were followed up to 24 weeks after treatment completion. Six of the 25 patients were evaluated as improved by the investigators at the end of four sessions, and at the 24-week post-treatment follow-up, four out of 25 were given a similar rating. The investigators observed clinical improvements in 60 percent, and patients in 44 percent, at four weeks after

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**PRACTICAL POINTER**

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treatment, but the figures decreased to 52 percent and 35 percent, respectively, at 24 weeks after treatment. Mean MASI scores decreased significantly from 7.6 to 6.2 (p=0.03). Mean melanin index decreased significantly after the first two sessions but relapsed slightly in subsequent follow-ups. Hyperpigmentation was observed in three of 23 patients (13 percent). The study pointed out the need for longer follow-ups to assess the efficacy of FP.

The Fraxel laser, which is FDA approved for the treatment of melasma, has not provided results as dramatic as those with CO₂ lasers. It is associated with a lesser downtime and decreased risk of complications. In darker skin tones, there is a higher risk of PIH when treating melasma patients. Naito conducted a study on six Chinese females who had resistant melasma. They were treated with FP at four-week intervals with a total of three to four sessions. Three patients improved by 50 percent, two by 30 percent and one by 20 percent. However, at the two-month follow-up, the mean improvement noted was only 35 percent.

Graber, et al. highlighted the low incidence of side effects with FP in their study involving 961 patients who were treated with Fraxel SR. Only 7.6 percent developed complications, the most common being acneiform eruptions (1.9 percent) and herpes simplex virus outbreaks (1.8 percent). There were no long-term sequelae.

In spite of this promising data, a recent review concluded that fluences and densities used for FP need to be conservative, as the risks for PIH remain. Treatments need to be conservative and placed at intervals of four to six weeks each. FP has shown potential in the treatment of therapy-resistant melasma, but more systematic studies with follow-up analyses need to be done.

**Erbium:YAG laser.** Erbium:YAG lasers emit light with a wavelength of 2,940nm that makes water its chromophore. It is highly absorbed by water-containing tissue, which helps the laser to ablate skin with minimal thermal damage.

Manalato, et al. evaluated the role of Er:YAG laser resurfacing in refractory melasma. Ten female patients with melasma unresponsive to previous therapy were included in this study. Full face skin resurfacing using an Er:YAG laser (2.94 microm) was performed using 5.1-7.6J/cm² energy. Adverse effects, such as prolonged erythema, infection, and hyperpigmentation, were recorded. The mean melanin reflectance spectrometry decreased from 48.8 to 43.6 at the six month follow-up. The mean MASI scores decreased from 19.1 to 10.6. Results showed definite improvement of melasma immediately after laser surgery; however, between three and six weeks postoperatively, there was universal development of post-inflammatory hyperpigmentation treated with topical azelaic acid, GA peels, and sunscreen.

Er:YAG lasers have shown favorable results in skin resurfacing with less downtime and more favorable side effects than other laser modalities. A variable square pulsed (VSP) Er:YAG laser was tested in the treatment of epidermal type melasma in 20 Thai women who received two passes at a fluence of 0.4 J/cm². Two treatments were given one month apart. There was a significant improvement in MASI score at the two-month visit from baseline (p=.004) but the improvement declined at the four-month follow-up (p=0.10). There was significant improvement in melanin index at the two-month follow-up (p=.02) but not at the four-month follow-up (p=.39). A total of 15 percent of patients had a 50-100 percent clearing of their melasma and 32.5 percent had a 26-50 percent clearing. Three patients developed mild PIH and two had acneiform eruptions. The square-shaped VSP Er:YAG pulses provide more controlled heating in an effort to maximize efficacy. The downtime observed with this modality is much less, and the secondary PIH that was observed healed within two weeks. However, the clinical efficacy of VSP Er:YAG is lower than that of FP.

**Q-Switched Lasers.** Several pigment lasers have been used to target melasma, as melanin has a wide absorption spectrum (500-1100nm). These lasers include the pigmented lesion pulsed dye laser (510nm), the Q-switched ruby laser (694nm), the Q-switched alexandrite laser (755nm) and the Q-switched Nd:YAG laser (1064nm).

Nouri, et al. designed a study to compare pulsed CO₂ laser alone with the combination of pulsed CO₂ laser followed by Q-switched alexandrite laser (Q-SAL) in the treatment of dermal-type melasma. The combination would mount a two-pronged attack by eliminating the superficial abnormal melanocytes and the hyperpigmented epidermis with the pulsed CO₂ laser and then target the denuded dermis with the deeper melanin using the Q-SAL. Eight patients with dermal-type melasma as diagnosed by Wood’s lamp examination were first given a two week course of tretinoin 0.05% cream, hydroquinone 4% cream, and hydrocortisone 1% cream, to be applied twice daily. The patients were randomized into groups of four and then one group was treated with one pass of the Coherent® 950 µsec pulsed CO₂ laser set at 300mJ/cm² followed by another pass with the Q-switched alexandrite pigmented dye laser at a fluence of 6J/cm². The other four patients were treated with the pulsed CO₂ laser alone. Patients were evaluated every four weeks for up to six months post-laser therapy. All four of the patients in the combination arm showed complete resolution without any peripheral hyperpigmentation. Those in the control group also showed complete resolution of melasma at the six month follow-up. No patient in the combination group showed any signs of hyperpigmentation at the more than...
six month follow-up; two patients in the CO\textsubscript{2} laser only group had peripheral hyperpigmentation in the long-term follow-up evaluation. A longer follow-up evaluation of these patients is needed to assess the efficacy of these two laser modalities. This study also lacked an objective parameter for measure of pigmentation.

Angsuwarangsee, et al. conducted a split-face designed study on six Thai females who were treated with combined Ultrapulse CO\textsubscript{2} laser (Lumenis) and QSAL on one side of the face and QSAL alone on the other side. These patients were suffering with refractory melasma. The rationale was to use an ablative laser to remove the excess epidermal melanin and abnormal melanocytes and then follow with a Q-switched laser to target the deeper melanocytes in the dermis without causing side effects. The patients were evaluated for up to six months. Their results indicated that the combined treatment had a statistically significant reduction of both the indices, whereas the side treated with just QSAL did not show significant results. Two of the six females developed severe PIH, and this was treated with 4% HQ three months after the laser treatment. There were no serious complications. Two patients had transient hypopigmentation and contact dermatitis on the combination side, which resolved spontaneously. The number of cases in this study is small, but the split-face design helps to overcome patient-to-patient variation. However, the study subjects did not have long-term follow-up.

QSAL has a longer wavelength of 755nm, which helps it to penetrate the dermis and target the dermal melanocytes. The Angsuwarangsee, et al. study supports previous reports on the ineffectiveness of Q-switch lasers alone in treating with dermal melanosis. Q-switch lasers target the melanosome as their chromophore, and if the melanocyte is in an inactive stage, or does not contain a melanosome, the Q-switch laser does not affect these cells.

The 1,064nm QS-Nd:YAG has a longer wavelength (>600nm), which is well absorbed by melanin. It is considered safer option in darker skin types as its lower energy spares injury to the epidermis. However, PIH with the use of the QS-Nd:YAG laser is still common in Asian skin types.

Wang, et al. reported results of their trial in which they combined low energy QS Nd: YAG and QSAL to treat patients with melasma. A total of 32 patients each rated their improvements according to the following scale: Pigment subsided by \( > \) or \( = \) 90 percent was regarded as “cured,” by 60-89 percent as “remarkably improved,” by 30-59 percent as “effective,” and by \( < \) 30 percent as “ineffective.” At the conclusion of this study, 21 patients (65.6 percent) rated themselves as cured after 10.2 +/- 3.5 times of treatments, 11 patients (34.4 percent) were remarkably improved after 11.4 +/- 2.5 times of treatment. The rates of “cured” and “remarkably improved” were 81.3 percent and 18.7 percent among patients with light brown melasma and 50.0 percent and 50.0 percent among patients with dark brown melasma (\( P < 0.05 \)). No patient suffered from hyperpigmentation or scarring; there was one episode of hypopigmentation. This study concluded that QS Nd: YAG and QSAL are safe modalities in those with skin of color, but the amount of pigment in lesions and disease course can change the treatment outcome.

Another study explored the effect of low-dose 1064nm Q-switched Nd:YAG laser (QSNYL) alone on melasma in 20 patients at fluences of 2.0-3.5 J/cm\textsuperscript{2}. The treatment was performed five times within a one-week interval. The L-value from the chromometer, which reflects the lightness of skin, was increased (0.86 +/- 1.67, \( p < 0.05 \)). The melanin

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<td>Zhou, et al.\textsuperscript{69}: Melasma areas imaged before treatment, after treatment, and at follow-up appointment. RCM showed decrease in bright melanin particle in basal layer and fewer melanin particles immediately after treatment. Repeat imaging in those patients with recurrence of melasma after treatment showed a return to baseline melanin levels. This lead to the conclusion that the results of this laser may be temporary.</td>
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<td>Yamashita, et al.\textsuperscript{70}: RCM images taken before and after IPL. Before IPL, increased signals indicated pigmentation presence. Following IPL, collapse of melanin caps with melanosome dispersal to keratinocytes seen. Melanosomes in epidermal basal layer rapidly migrated to surface</td>
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index from the mexameter was significantly decreased (-28.23 +/- 28.21, p < 0.001). The study concluded that low-dose 1064nm QS-Nd:YAG appeared to be an effective treatment modality for melasma.52

The usefulness of Nd:YAG laser has been challenged due to side effects and comparable results to topical treatments. Wattankrai, et al. conducted a split-face randomized study comparing the combination of QS-Nd:YAG laser and 2% hydroquinone with topical treatment in dermal or mixed-type melasma. The study consisted of 22 patients who were treated with 1,064nm QS-Nd:YAG laser, 6mm spot size, 3.0- to 3.8-J/cm² fluence for five sessions at one-week intervals. After five laser treatments, the colorimeter readings showed that the laser side improved by an average of 94.5 percent in relative lightness index compared to 19.7 percent of those using HQ. The mMASI score for the laser side improved by 72.5 percent, compared to 24 percent in the control group. Both these results represented a statistically significant improvement (p<0.001) at the three month follow-up. All patients had a recurrence, and four out of 22 patients had rebound hyperpigmentation. After the five laser treatments, 13.6 percent (three of 22 patients) had developed mottled hypopigmentation that gradually improved. The laser treatment was associated with significant side effects. More than five treatments weekly were advised, with clinician evaluation for the development of any hypopigmentation or leukoderma, which contraindicate further treatments.53

The effects of the Nd:YAG laser have also been assessed by reflectance confocal microscopy imaging before and after treatment. In a study conducted by Zhou, et al., 50 patients were given nine weekly Nd:YAG laser treatments. Follow-up was conducted at three months after the completion of the treatments. Effectiveness of treatment was measured by MASI scores and confocal microscopy. At the end of the nine treatments, there was a mean decrease in MASI score of 61.3 percent. A more than 50 percent improvement was achieved by 70 percent of patients with 10 percent of patients reporting a 100 percent improvement. At three month follow-up melasma had recurred in 64 percent of patients. Before Nd:YAG laser, RCM imaging of affected areas yielded multiple melanin particles in keratinocytes in the lower stratum spinosum and basal layers, creating “melanin caps.” Interspersed in the basal layer were large bright melanocytes. After the treatments, RCM imaging of treated areas showed fewer melanin particles and the large melanin particle previously in the basal layer were rarely found. Melanin level appeared to return to baseline in those patients who had a recurrence at the three month follow-up. These findings were indicative of the mechanism of action of Nd:YAG lasers, which is an inhibition of melanin formation in melanocytes and decreased transfer of melanin from melanocytes to keratinocytes. Because of the high recurrence rate and presence of increased melanin levels in these patients on RCM, the effects of Nd:YAG may just be temporary.54

**Intense Pulsed Light.** Intense Pulsed Light (IPL) is a broadband light source that emits a continuous spectrum in the range of 515-1200nm. Yamashita, et al. studied the photothermal effect of IPL using reflectance-mode confocal microscopy (RCM) and optical coherence tomography (OCT). RCM was used before and after IPL therapy. Images done prior to IPL showed higher reflectance signals in comparison to surrounding skin, representing the increase in pigment concentration. After IPL, RCM images showed a collapse of the melanin caps with dispersal of melanosomes among the basal keratinocytes. The study showed that melanosomes in the epidermal basal layer rapidly migrated to the skin surface. The IPL therapy had caused the denaturation of melanin caps-containing cells that had triggered the differentiation of basal keratinocytes that would replace those extruded. The IPL irradiated melanocytes in the lesions were left intact and resumed their activity after treatment. The authors concluded that IPL therapy needs to be combined with bleaching agents or Q-switched laser for suppression of melanocytes.55

Li, et al. enrolled 89 Chinese women with melasma to study the efficacy and safety of IPL. Eighty-one percent of the patients had a mixed type melasma, and 19 percent had epidermal type according to Wood’s lamp examination. The patients received a total of four treatments at three week intervals at an energy density of 13 to 17J/cm², which was adjusted according to the skin type. Sixty-seven of 89 patients (75.3 percent) obtained 51 to 100 percent improvement after four IPL sessions, according to the overall evaluation by dermatologists, and this number rose to 69 at the three month follow-up (77.5 percent). According to patient self-assessments, 65 of 89 patients noted improvement by 50 percent or more at the end of the trial, and 63 (70.8 percent) maintained this result at follow-up. The mean MASI scores decreased significantly from 15.2 to 5.2 after four sessions. All of the parameters were reassessed at the three-month follow-up. The mean MASI score was 4.5 at the follow-up visit (p<0.01). Melanin Index (MI) decreased from 140.8 at baseline to 121.1 after four sessions and was 119.7 at the 3-month follow-up visit (p<0.001). Patients with epidermal-type melasma responded better to treatment than mixed type. The study concluded that the therapeutic efficacy of IPL increases in epidermal-type melasma and if the underlying hormonal etiology is absent. It also showed that results achieved with IPL are maintained consistently up to three months after cessation of therapy.56

In another study conducted by Zhou, et al., 38 patients were treated with IPL for three to five sessions at 40-45
day intervals. Patients received follow-up at 30 days, three months, six months, and some at even more than one year. Improvement was graded based upon reductions of hyperpigmented areas and decrease of dark tones, with 80-100 percent reduction graded as excellent, 60-79 percent reduction graded as good, 40-59 percent reduction graded as moderate, and <39 percent reduction graded as poor. At the end of the study, 18 patients were graded as excellent, 11 as good, five as moderate, and four as poor. In the cases graded poor, hyperpigmented areas returned within two to four months. No side effects were reported at the end of four to five treatments.54

**DISCUSSION**

Based upon studies available that addressed long-term results, IPL provided long-lasting laser treatment for melasma. Few physicians use these methods in clinical practice due to side effects. IPL is known to cause scarring and erythema in darker skinned people. Although the IPL studies conducted were limited by the number of participants and by the limited time frame for follow-up, the use of these treatment modalities should be further explored.

In addition, this literature review yielded very few studies using confocal microscopy to assess treatment efficacy. In the above listed categories, RCM evaluation of melasma site before and after treatment were only seen in the use of IPL and Nd:Yag lasers. In addition, the ability of RCM to better stratify melasma patients into groups based upon depth of deposition of pigment will aid in choosing the laser best suited for the patient. RCM can also offer insight of the effects of laser treatments through serial imaging and assessment, which would be difficult to achieve with biopsies because of location of melasma lesions predominantly on the face. This offers the ability to analyze the mechanism by which these lasers work at a cellular level and whether their mechanism offers a long-term or short-term treatment of melasma. When patients are refractory to many treatments, it becomes beneficial to advise a patient to have a noninvasive imaging assessment in order to understand the pathophysiology of their lesions.

An important point in the treatment of melasma is the customization of treatments for each patient. The plethora of treatments available is a result of their variable usefulness for melasma. Finding treatment for each patient while taking into account their melasma type and how each type has responded to treatments in the patient’s past is important when making a treatment plan. Because of the exacerbating effects of the sun on melasma, it is necessary to counsel patients on the need for adequate sun protection and sun avoidance in order to maintain results from various treatments for as long as possible.

Melasma is a difficult skin condition to treat. Future studies must focus on assessing the long-term results of the currently available and widely used treatments.

**CONCLUSION**

Lasers are another treatment option for patients with melasma refractory to topical treatment. While many topical treatments exist that are inexpensive and have minimal side effects, laser therapy is both expensive and ridden with potential adverse effects. Careful measures must be taken prior to choosing the appropriate laser as well as during therapy. The use of RCM to better classify melasma type as well as choose the most appropriate laser is underutilized and would greatly help in minimizing adverse effects. Its use will help in providing the most precise and customizable level of care.

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