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Melasma: Which Laser and Light Therapies Achieve Long Lasting Results? A Review of the Literature Over the Last 30 Years

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Abstract

Background: Melasma often presents as a therapeutic challenge to dermatologists. Due to its relapsing nature, long-term topical maintenance therapies are often required which may be time consuming and costly for patients. As a result, light and laser therapies have become increasingly popular in the treatment of melasma. Yet, clinical studies on melasma tend to focus more on the efficacy of these treatments rather than their ability to achieve long-term results.

Objective: To assess the ability of light and laser treatments to achieve long lasting results in melasma.

Methods: A literature review was conducted to assess the long-term efficacy of laser and light treatments in epidermal, mixed and dermal melasma.

Results: Out of 128 articles reviewed, 17 studies of laser and light therapies included patient follow-up without maintenance therapies in their study designs. According to these studies, IPL and Nd:YAG achieved long lasting results for up to 6-months. Studies also suggest that combining these therapies together as well as combining them with other topical or procedural therapies, may result in enhanced long-term efficacy. Despite this, these treatments are less commonly used than topical therapies in clinical practice due to their cost and potential side effects, such as scarring, post inflammatory hyperpigmentation and prolonged erythema. Studies also indicate that these therapies vary in efficacy depending on the melasma subtype.

Limitations: There was a lack of standardized outcome assessments.

Conclusions: In conclusion, light and laser treatments have a role in treating melasma. To study their efficacy in treating melasma long-term, more studies with extended duration of follow-ups and standardized outcome measures are needed.

Keywords: Melasma; Laser; Intense pulsed light; Fractional photothermolysis

Introduction

Melasma is a common acquired disorder that is characterized by hyperpigmented macules or patches that tend to occur symmetrically in sun-exposed areas, more frequently in women [1]. The pathogenesis of melasma is not fully known, but it is widely accepted that ultraviolet light exposure, hormones and genetic predisposition contribute as causative and exacerbating factors [2]. Histologically, melasma can be divided into epidermal, dermal or mixed types based on the degree of melanin deposition in the skin. Traditionally, Wood's lamp examination has been used for distinction between the melasma types. More recently, reflectance confocal microscopy has been proposed as an alternative modality.

Despite being a common diagnosis, melasma is typically difficult to treat and often has a negative impact on a patient's psychological well-being [3]. A key challenge in treating melasma is its relapsing course with frequent recurrences. Frequently, long-term maintenance therapies are required that may be costly and time consuming. Topical therapies, such as triple combination cream, are currently considered first-line for the treatment of melasma, yet they have marginal efficacy and are typically more beneficial for epidermal type melisma [3]. In addition, previous studies have suggested that the median time to melasma relapse following cessation of triple combination cream was 58 days [4]. As a result, many alternative treatment modalities have been developed [1,3]. Light and laser therapies, though expensive, have become increasingly popular in the treatment of melasma. Laser therapy, which targets both dermal and epidermal melanin, seems to be somewhat effective in the treatment of all types of melisma [5]. Although many studies have reported the short-term effectiveness of these treatments, the duration of their efficacy has not been frequently studied. Furthermore, many studies are confounded by the use of topical maintenance therapies during follow-up intervals. This leads to inaccurate reporting of the long-term efficacy of many therapeutic modalities. Also, few studies have analyzed the type of melasma when evaluating the efficacy of these treatments. Herein, we review the ability of laser and light therapies to achieve long-term disease free intervals, with special focus on the three different melasma subtypes.

Methods

Study selection

A literature search using MEDLINE, ScienceDirect, Scopus and Ovid was conducted using the key words "melasma", "recalcitrant melasma", "intense pulsed light" and "laser". Additionally, a filter for peer-reviewed studies in academic journals was used. We included

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studies from the past 30 years that were published in English. On review, a total of 128 articles were screened for eligibility. The inclusion criteria was: (1) the aim of the study was to analyze the efficacy or safety of a laser or light treatment for melasma, (2) the intervention consisted of any type of laser or light treatment, with no comparison required, (3) study was either a randomized controlled trial, retrospective or a prospective cohort study. Study designs that were case reports or review articles were excluded from our analysis. Studies were also excluded if patients were receiving/undergoing maintenance therapies, such as topical creams, as this would confound the results. All potentially relevant studies were retrieved as full articles.

Data extraction

Data was extracted from full texts with a standardized list. The data derived from the articles included items such as the authors, treatment modality, duration or number of treatments, melasma classification, follow-up period, method for evaluating the results, and results of the study. The methods for evaluating results in studies included: clinical improvement as determined by dermatologists, patient assessment/questionnaires, Melasma Area and Severity Index (MASI), the modified MASI (mMASI), recurrence rates, reflectance spectrophotometer melanin measurements (melanin index), Visual Analog Scale (VAS), and colorimetery. For the purpose of our study, laser treatments as monotherapy and laser/light therapies in combination with other modalities (microdermabrasion, other lasers/light therapies, or topical therapy) were analyzed separately.

Results

Intense pulsed light

Intense pulsed light (IPL) is a broadband light source that emits a continuous spectrum in the range of 515-1200 nm [6]. Many recent studies have yielded some promising results with IPL in inducing the remission of melasma. Li et al. studied 89 patients treated with 4 sessions of IPL and included a 3- month post treatment follow-up [7]. Eighty-one percent of the patients had mixed type melasma and 19% had epidermal type according to Wood's lamp examination. At follow-up patients were assessed for the clinical improvement, patient-reported improvement, MASI score reduction, and melanin index [7]. At 3-months, 77.5% of patients had a greater than 50% clinical improvement as determined by the study physicians. In support of this, 70.8% of patients reported a greater than 50% improvement. The MASI score decreased from an average of 15.2 at baseline to 4.5 at the 3-month follow-up. The melanin index decreased from 140.8 at baseline to 119.7 as well [7]. The results indicate that IPL's efficacy is maintained for up to 3-months following treatment. Patients with epidermal-type melasma responded better than mixed-type and the authors concluded that IPL's therapeutic effect increases in epidermal type melisma [7].

Q-switched lasers

QS lasers deliver short nanosecond pulses of energy to the skin aimed to selectively target melanosomes with thermal diffusion [8]. The thermal relaxation time of melanosomes ranges from 50 to 500 ns and the absorption spectrum of melanin is broad ranging from 500-1100-nm. As a result, several Q-switched (QS) lasers have been used in melasma at various wavelengths, including QS Nd:YAG (1064 nm), QS Ruby laser (694 nm) and the QS Alexandrite laser (755 nm). The QS Ruby laser (694 nm) will be discussed under fractional photothermolysis.

QS-Nd:YAG

The 1064 nm QS-Nd:YAG, with a long wavelength, has deep skin penetration and is useful at targeting dermal melanin. The long wavelength also makes it a safer option in darker skin types because it minimizes epidermal injury. Nd:YAG has also recently shown to induce long lasting results. Vachiramon et al. compared 10 patients with mixed type melasma treated with 5 sessions of Nd:YAG monotherapy to Nd:YAG combined with IPL [6]. In the Nd:YAG monotherapy cohort, the recurrence rate at 3-months post treatment, as defined as an increase in the mMASI score by 50% as compared to the end of the treatment interval, was only 11% [6]. Further, 23 Korean patients (19 with mixed and 4 with epidermal type) with a baseline MASI of 14.15 +/- 1.47 were evaluated following 10 treatments of QS Nd:YAG. Treatment resulted in a MASI of 8.22+/- 2.9 and 10.15 +/- 2.7 at the 1 and 3-month follow-ups respectively [9]. The authors of this study concluded that QS Nd:YAG laser was safe and effective for mixed-type melasma.

Still, Nd:YAG's usefulness has been challenged recently. One study using Nd:YAG reported that the evidence of melasma flare was "common" at 3 months, however failed to define how recurrence was reported [10]. The study included patients with both epidermal and mixed type melasma but did not report the proportion of patients with each subtype. One study by Moubasher et al. compared treatment with varying strengths of TCA chemical peels to the treatment of double frequency QS Nd:YAG. Patients were treated with 20%, 25%, or 30% TCA peeling for 8 treatments at 2-week intervals. The greatest reduction in MASI score was seen in the patients treated with TCA 25% [11]. However, at the 3-month follow-up, 32% of patients had recurrences, regardless of being treated with TCA peeling or Nd:YAG [11]. The authors included epidermal, mixed and dermal types of melasma in the TCA cohorts but failed to identify the subtypes of melasma in the Nd:YAG cohort. They concluded however, that TCA is more effective at treating melasma than Nd:YAG and had fewer incidences of complications such as post inflammatory hyperpigmentation.

The Nd:YAG has also been combined with many other treatment modalities. Multiple studies evaluated the efficacy of IPL, which is known to be more beneficial in epidermal melasma, in conjunction with Nd:YAG. Yun et al. studied 12 patients treated with this combination for 6 sessions and evaluated them at 2-months. The authors did not specify the subtypes of melasma in their subjects. MASI decreased by 47% after 1 month and 50% after 2 months [8]. IPL alone resulted in a 24% decrease in MASI after 2-months [8]. The authors suggested that the combination of these treatments may have superior efficacy for long-term remission. Another similar study by Na et al. reported that combining IPL with Q-switched Nd:YAG provides more rapid results than IPL alone and also resulted in an average of 5.9 months of disease free clearance in patients with mixed-typed melisma [12]. Chung et al. completed a split-faced study of 61 patients with half of their face treated with combined IPL and Nd:YAG and the other with pulsed –in pulsed IPL only. He conducted a 6-month follow up via patient questionnaires and found no serious aggravation of melasma for 6 months after the last treatment on either side of patients' faces [13]. Yet, on contrary to the previously mentioned studies, he found no statistical difference between pulsed-in pulsed IPL alone versus combined IPL and Nd:YAG. This study, however did not categorize subjects by their melasma subtype as well.

Topical therapies in combination with laser therapies such as Nd:YAG are also frequently evaluated. A study done by Fabi et al. on the efficacy of Nd:YAG compared to Alexandrite laser suggested

that combining triple combination cream with Nd:YAG in patients with moderate-severe mixed type melasma may be effective for up to 3-months. Treatment with Nd:YAG combined with triple combination cream assessed at 3 months post treatment and discontinuation of topical therapy resulted in a 27% reduction in the mMASI score on average [14]. Furthermore, another study included microdermabrasion with this regimen. Eight patients with undefined melasma types were treated with combined microdermabrasion, triple combination cream and Nd:YAG laser of varying pulse widths (5 ns versus 50 ns). This regimen resulted in a decrease in the MASI score and melanin index that lasted up to 6-months [15].

QS ALEXANDRITE

The 755 nm QS Alexandrite laser's use in the treatment of melasma has been more controversial than that of the Nd:YAG's. More caution is typically advised when using the QS-Alexandrite laser because the 755 nm wavelength allows it to be more readily absorbed by melanin and therefore, it has a higher risk of adverse events [14]. Still, a previously mention study by Fabi et al. suggested that the 755-nm alexandrite laser in combination with triple combination cream may be as equally effective as the Nd:YAG in the treatment of moderate to severe mixed melasma. Mixed type melasma patients treated with the Alexandrite laser had a 19% reduction in the mMASI at 3 months [14]. In addition, no serious adverse events were observed in either cohort, with only one patient in each group experiencing post-inflammatory hyperpigmentation.

Fractional photothermolysis

Many lasers also incorporate the concept of fractional photothermolysis in the treatment of melasma. Fractional photothermolysis involves emission of light into "microthermal zones" or three-dimensional zones of thermal damage that induce epidermal repair [16]. Lasers of this modality included in our discussion are the 1550-nm erbium doped fractional laser, 1410-nm fractional laser, 1927-nm thulium laser, 1540-nm erbium-glass laser, and the QS Ruby fractional laser.

The ability of fractional lasers to induce long-term improvement in melasma has resulted in controversial results. Wanitphakdeedecha et al. evaluated the MASI score, melanin index and VAS score at 3 months post treatment with 5 sessions of 1410 nm fractional photothermolysis in 30 patients [17]. The authors found that fractional photothermolysis resulted in statistically significant reduction in these three melasma severity scores for 3-months. Specifically, the MMASI score decreased from 9.7 pretreatment to 4.4, the melanin index decreased from 240 to 195 and the VAS decreased from 73 to 23 [17]. They did not classify the subjects into melasma types. Similarly, Massaki et al. treated 20 patients with one treatment of 1,927-nm fractionated thulium laser and reported that the MASI decreased from an average of 13.2+/-5.4 at baseline to 8.5+/- 3.5 and 6.1 +/- 5.6 at 1 and 6-12 months respectively [18]. These authors also reported that only 7 out of 15 patients had a recurrence in an average of 10.2 months and alluded to the ability of the fractional 1,927-nm thulium laser to induce long-term remission [18]. Again, these authors did not classify melasma patients into their subtypes.

On the contrary, Karsai et al. studied 51 patients without mention of melasma subtype and compared the use of sunscreen alone to sunscreen in combination with non-ablative 1550-nm fractional photothermolysis. At 3-months follow-up, they found the MASI score was reduced in both groups. However, a more significant reduction in the MASI score was seen in the group treated with sunscreen alone and may indicate that non-ablative fractionated photothermolysis may not provide a substantial benefit in treating melisma [19]. Yet, the authors suggested that their results might have been biased due to the higher baseline MASI in the control group [19].

Despite these conflicting results, Kroon et al. compared triple combination therapy to nonablative fractional photothermolysis and found that the recurrence rates of both groups were similar [20]. The MASI and melanin index showed no significant statistical difference between groups. Although the nonablative fractional photothermolysis group had more short-term side effects, patients in this group were significantly more satisfied. The authors ultimately suggested that 1550-nm fractional laser was safe and comparable in efficacy and recurrence rate with triple topical therapy.

Further, a recent split faced study also compared 10 treatments with Nd:YAG alone to Nd:YAG in combination with 1550-nm erbium doped fractional photothermolysis. This study reported both interventions resulted in a sustained reduction in the mMASI score and there was no statistical difference between the groups. In the Nd:YAG group, there was a 59.3% reduction in mMASI at the 3-month follow up whereas the combined group had a 58% reduction at 3 months [21]. The authors failed to identify the melasma subtype in both cohorts (Table 1).

The efficacy of the 694-nm QS Ruby fractional laser in melasma treatment, like many of the other fractional lasers, is still controversial. Like the QS-Nd:YAG, it causes selective destruction of melanosomes. As a result of its shorter wavelength, it is thought to be more selective for melanin. However, it also results in more superficial absorption and increases the risk of adverse events. As a result, fractional-mode has been used to minimize this risk. A study of the 694-nm Q-switched Ruby fractional laser in 25 patients with either epidermal or mixed-type melasma found that the MASI reduced from 6.54 at baseline to 1.98 at 1-month follow-up. The authors reported that 7 patients (28%) had recurrence of melasma at 3-months. Further, post inflammatory hyperpigmentation (PIH) occurred in 11 patients (44%). The authors suggested the laser was effective to treat melasma but significant PIH and recurrence of melasma was evident at 3 months and may reduce patient satisfaction [22].

Discussion

In our study, various laser and light treatments and numerous combinations of these with other melasma therapies resulted in varying disease free intervals. Studies on IPL and Nd:YAG suggested prolonged maintenance of therapeutic results ranging between 2 to 6 months [7,8,12,13]. Despite Nd:YAG's and IPL's proven efficacy, these treatments are often not used in clinical practice due to cost and concerns for significant side effects including post-inflammatory hyperpigmentation, scarring, and erythema, especially in patients with darker skin types. Still, it may be necessary to weigh the risk of adverse events to their potential benefits in inducing long-term improvement of melasma. This is especially true in patients who have failed multiple therapies previously or who are unable to be compliant with long term maintenance therapies that tend to be costly and time consuming.

Unlike Nd:YAG and IPL, the role of fractional photothermolysis in the treatment of melasma still remains largely controversial and studies on its efficacy have yielded mixed results. Many of these studies failed to define the melasma subtype in their subjects. It is necessary that large scale, randomized controlled trials are conducted in order to appropriately define its role in treating melasma.

Notably, our analysis includes a wide heterogeneity of studies,

Author	Patients	Type of Melasma	Intervention	Length of follow-up	Outcome Criteria	Results
Li	89	72 mixed 17 epidermal	IPL, 4 treatments at 13-17 J/cm^2	3 months	1. Clinical improvement 2. Patient reported 3. MASI score 4. Melanin Index	Clinical improvement: 77.5% with > 50% improvement at 3-months 70.8% reported >50% improvement at 3-months MASI decreased from 15.2 at baseline to 4.5 at 3-months Melanin Index decreased from 140.8 at baseline to 119.7 at 3-months
Vachiramon	20	20 Mixed	10 patients with Nd:YAG for 5 treatments + IPL for 3 treatments 10 patients with Nd:YAG alone for 5 treatments	3 months	1. Recurrence rate (defined as increase in mMASI score by 50% from the post treatment mMASI score)	Combined side: Recurrence rate of 33% at 3 months Nd:YAG monotherapy: Recurrence rate of 11% at 3 months
Suh	23	19 mixed 4 epidermal	QS-Nd:YAG for 10 treatments	1 month 2 months 3 months	1. MASI 2. Colorimetry (mean lightness)	MASI reduced from 14.15 baseline to 8.22, 8.95, & 10.15 at 1, 2 and 3-months Mean lightness improved from 60.71 to 61.73, 61.59, 61.29 at 1, 2, and 3-months
Brown	20	Epidermal or mixed	QS-Nd:YAG	3 months	1. Recurrence rate	Recurrence: evidence of melasma flare was “common” at 3 months
Moubasher	65	Epidermal, Mixed and Dermal in TCA groups Undefined in laser group	50 patients treated with TCA 15 patients treated with double frequency QS-Nd:YAG	3 month	1. Recurrence rate	Recurrence rate: 32% at 3 months
Na	62	62 mixed	31 treated with IPL once followed by Nd:YAG for 4 treatments 31 treated with Nd:YAG alone for 5 treatments	5.9 months (average)	1. Patient questionnaire	Combination of IPL and Nd:YAG: No further treatments required IPL alone: 5 patients presented for further treatment with IPL for satisfactory results
Yun	24	unknown	12 patients treated with combined IPL + QS-Nd:YAG for 6 treatments 12 patients treated with IPL only for 6 treatments	2 months	1. MASI score	Combined group: MASI decreased by 47% after 1 month, and 50% after 2 months IPL only group: MASI decreased by 15% after 1 month, and 24% after 2 months
Chung	61	unknown	Split faced: ½ face treated with IPL once + Nd:YAG for 6 treatments ½ face treated with pulsed-in pulsed IPL for 7 treatments	6 months	1. Patient questionnaire	Both sides: No serious aggravation of melasma for 6-months after the last treatment No statistically significant differences were found between the treated sides
Fabi	20	20 mixed	Split faced: ½ face treated with Nd:YAG for 6 treatments combined with triple combination cream ½ face treated with Alexandrite laser for 6 treatments combined with triple combination cream	2 week 3 months 6 months	1. mMASI	Nd:YAG + triple combination cream: 36% reduction in mMASI score at 2-weeks 27% reduction in mMASI score at 3-months 27% reduction in mMASI score at 6-months Alexandrite + triple combination cream: 44% reduction in mMASI score at 2-weeks 24% reduction in mMASI score at 3-months 19% reduction in mMASI score at 6-months

Salman	8	unknown	split faced: ½ face with 3 laser treatments 1 month intervals (either 50 ns or 5ns Q switched Nd:YAG) Combined with microdermabrasion and topical therapy	3 months 6 months	1. MASI score 2. Reflectance spectrophotometer melanin measurements	50 ns QS-Nd:YAG MASI at 1 month: 35% reduction MASI at 6 months: 28% reduction Melanin measurements at 1 month: 20% reduction Melanin measurements at 6 months: 10% reduction 5 ns QS-Nd:YAG MASI at 1 month: 28% reduction MASI at 6 month: 23% reduction Melanin measurements at 1 month: 17% reduction Melanin measurements at 6 month: 12% reduction
Karsai	51	unknown	Either sunscreen alone or sunscreen in combination with 4 treatments non-ablative fractional photothermolysis	3 months	1. MASI	Sunscreen alone: MASI decreased from 4.8+- 1.8 to 3.4+/-1.7 at 3-months Non-ablative fractional photothermolysis: MASI decreased from 2.5+/-1.9 to 1.9+/-1.8 at 3-months
Hilton	25	Epidermal or mixed	Q-S Ruby fractional laser 1-3 treatments	3 month	1. MASI 2. Recurrence Rate	MASI: Reduced from 6.54 to 1.98 at 1-month Recurrence rate: 7 patients (28%) had recurrence of melasma
Tourlaki	76	unknown	4 treatments of fractional 1540 nm erbium-glass laser in combination with triple combination cream	1 month 6 months	1. MASI	67.1% had a >75% reduction in MASI at 1-month 21% had a 51-75% reduction in MASI at 1-month 21.1% had a >75% reduction in MASI at 6-months 43.4% had no improvement in MASI score at 6-months
Kroon	10	1 mixed 3 dermal 6 epidermal	4 treatments of 1550-nm nonablative fractional laser	3 months 6 months	1. Physician global improvement scale (Scale of 1-6; 0= 100% improvement vs. 6= worsening of hyperpigmentation) 2. MASI 3. Recurrence rate	3-month global improvement: 5.8 +/- 2.3 6-month global improvement: 4.4 +/- 3.1 MASI went from 8.5 +/1 3.6 to 8.7 +/- 5.5 and 18.0 +/- 10.4 at 3 and 6 months respectively 5 patients had recurrence after 6 months.

Abbreviations: MASI: Melasma Area and Severity Index; mMASI: modified Melasma Area and Severity Index; VAS: Visual Analog Scale

Table 1: Studies that evaluated the long-term efficacy of laser and light treatments for the treatment of melasma.

which makes it difficult to compare treatments. Generally, there is a lack of well-designed, placebo-controlled comparative studies. Many of the studies included in our analysis had small patient populations and several studies also used subjective measures such as patient assessment of improvement to report efficacy at follow-up. In addition, many studies report the percent of patients that experience "recurrence" at follow-up but few define the criteria for "recurrence". Standardization of outcome measures is necessary at follow-up in order to effectively compare treatment modalities. Since the mMASI has recently been validated and revised, we recommend future studies to use this scoring system to evaluate patients at follow-up [23,24].

Also, few studies identified in our analysis followed patients for longer than 6-months. More large-scale studies need to be completed that include longer follow-up in their study designs in order to further evaluate the duration of therapeutic results as well as the average time to disease recurrence. Further, more studies should exclude the use of maintenance therapies in their follow-up intervals in order to assess the ability of therapies to achieve long lasting results in a more accurate way. It is also important that the melasma subtype is defined in future study designs, as it is now known that response to a specific treatment modality may vary depending on melasma subtype.

Special consideration should be given to the subtype of melasma affecting a particular patient when considering the appropriate therapy. Previous studies have found that epidermal melasma tends to respond better to superficial peels, topical therapies and IPL. Whereas, mixed or dermal type melasma tend to respond better to laser therapies, in particular the Nd:YAG. Furthermore, combining therapies that target both epidermal and mixed type melasma may be even more efficacious and prolong the duration of therapeutic results. Wood's light examination, which is infrequently used in clinical practice, may be useful in characterizing melasma into its subtype when choosing the appropriate therapy. In addition to Wood's light exam, reflectance confocal microscopy has recently been proposed as a non-invasive means to evaluate melisma [16].

Conclusion

Melasma is a chronic relapsing disease with significant psychological impact. Often patients require long-term topical maintenance therapies that, though proven effective, can become costly and time consuming. Despite topical regimens being "gold standard", once discontinued these treatments may result in rapid recurrences once discontinued. In our review, good results were achieved with IPL and Nd:YAG for up to 6-months. Long-term studies beyond 6-months with standardized outcome assessments, however, may be necessary to better quantify the relapse rates with these treatments. It is also of utmost importance to consider the melasma subtype when choosing melasma treatments.

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