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Melasma: A critical analysis of clinical trials investigating treatment modalities published in the past 10 years

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Abstract

Background: Melasma is an acquired disorder of facial pigmentation which is a treatment challenge.

Aims: The aim of this article is to critically appraise the clinical trial evidence for different treatment modalities for melasma, published in peer-reviewed journals in the past 10 years.

Patients/Methods: The literature review was conducted using PubMed and MEDLINE. The search was performed in July 2019, and search parameters were limited to all English language articles published in the past 10 years only.

Results: Eighty-nine clinical trials were found. Four clinical trials investigated topical hydroquinone, supporting its safety and efficacy as first-line treatment. Twelve studies showed tranexamic acid as very promising. Nineteen studies assessed various novel oral, injectable, and topical treatments and highlight some new potential future treatments. Forty-two studies investigated laser and light treatment in melasma: LFQS laser is still one of the best options, especially in darker skin types. However, the picosecond laser has shown excellent results. Finally, 11 studies looked at peels. Overall, peels have not been shown to be superior to the use of topical therapy alone.

Conclusion: Topical therapy with a HQ and retinoid-based product should be first line for a minimum of 3 months with the addition of oral tranexamic acid at 250 mg BD if no contraindication. Second-line treatment with lasers includes the LFQS Nd:YAG, picosecond laser, and the pulsed dye laser in lighter skin types. Third-line therapy would be the addition of chemical peels to the above treatments, with GA or TCA peels having the most evidence for effectiveness.

KEYWORDS

hydroquinone, melasma, pigmentation, tranexamic acid, tretinoin

1 | INTRODUCTION

Melasma is a common, acquired disorder of facial pigmentation which poses one of the greatest treatment challenges to the dermatologist and the aesthetic practitioner. Clinically, it is characterized by irregular brown macules and patches on the face.[1]

The exact cause is unknown but risk factors for melasma are well-established and include a history of sun exposure as well as exposure to visible light, Fitzpatrick skin types greater than III, pregnancy, the use of exogenous hormones such as the oral contraceptive pill and hormone replacement therapy, as well as a family history.[2] There is also emerging evidence for a significant vascular component in

melasma lesions; affected skin has an increased density of dermal blood vessels compared to normal perilesional skin.

Although melasma is asymptomatic, it is a disfiguring skin disease that has a negative impact on quality of life and the self-esteem of affected individuals.[2] Though the majority of cases affect females, males still account for <20% of cases.[3]

A vast array of treatments and combination treatments have been tried in an effort to "cure" melasma, and the sheer number of options is a clear indication that no single modality or even combined modalities have been shown as being truly effective. Generally, regardless of treatment modality or modalities, response is unpredictable and relapse frequently occurs, even if improvement is initially seen.

2 | ESTABLISHED TREATMENTS

2.1 | Photoprotection

First and foremost, the most well-established method of controlling melasma and potentially preventing it from worsening is vigilant photoprotection. In 2010, it became established that both UV light and visible light can cause sustained worsening of pigmentation in all skin types, especially darker skin types.[4] This fact provides justification for the recommendation of daily use of physical sunscreen agents, like titanium dioxide and zinc oxide, rather than chemical agents which are not able to protect against the damage from visible light.[5]

2.2 | Hydroquinone

Hydroquinone (HQ) is considered first-line treatment for melasma, and there is a strong evidence base for its use. It was first found to be a bleaching agent in 1936 and, in 2010, it was reported that in the United States alone, there were 10-15 million tubes of HQ sold annually.[6] HQ is chemically known as 1,4-dihydroxybenzene and works by inhibiting the tyrosinase enzyme in the production of melanin.

2.3 | Triple combination creams

In 1975, Kligman and Wills proposed the use of a combination therapy known today as Kligman's Solution: HQ 5%, tretinoin 0.1%, and dexamethasone 0.1%. Topical retinoids are a class of vitamin A derivatives which potentially also have the ability to inhibit the tyrosinase enzyme while also accelerating epidermal turnover and dispersing the pigment granules in keratinocytes.[7] This triple combination cream has been found to be a very effective treatment for melasma and has been altered over the years to produce a less irritating combination, while maintaining or improving efficacy. The most recent combination is known as Tri-Luma (HQ 4%, tretinoin 0.05%, 0.1% fluocinolone acetonide) in the United States and is FDA-approved for the treatment for melasma.[7]

2.4 | FDA-approved laser treatments for melasma

In 2005, the United States (US) Food and Drug Administration (FDA) approved the nonablative fractional 1550/1540 nm laser for the treatment of melasma. The midinfrared wavelengths are thought to bypass the epidermis and penetrate the mid-reticular dermis to stimulate remodeling and neocollagenesis, while at the same time facilitating the removal of dermal melanophages via transepidermal elimination.[8]

In 2012, the FDA-approved Lutronic's Spectra laser, the first and only Q-switched laser therapy for the treatment of patients with melasma.[8] In theory, lasers and light should be effective at treating melasma, as melanin has a broad absorption spectrum (630-1100 nm) making it amenable potentially to a variety of laser and light sources. Melanosomes have short thermal relaxation time of 50-500 ns. It is understood that longer wavelengths can penetrate deeper to reach dermal pigment but melanin absorption is better at shorter wavelengths.

3 | METHODS

3.1 | Aims and objectives

The aim of this paper is to critically appraise the clinical trial evidence for different treatment modalities for melasma, published in peer-reviewed journals in the past 10 years. The primary outcome of interest is efficacy, especially as compared to the established standard treatments, with safety being a secondary consideration with certain treatments.

3.2 | Method

The literature review was conducted using PubMed and MEDLINE. In order to identify all relevant articles, Mesh terms where combined with key text terms. The following search terms were used to identify articles:

(Melasma) AND Treatment AND Clinical Trial[ptyp] AND "last 10 years"[PDat] AND Humans[Mesh] AND English[lang].

The search was performed in July 2019, and search parameters were limited to all English language articles published in the past 10 years only (from 2009). The main aim was to find information about efficacy of the various methods as compared to other treatments or to vehicle or placebo. "Best Match" sort order was used.

One-hundred seventy-four articles were found via the literature search (Figure 1). The articles were then screened on the basis of title and abstract to remove unrelated articles. Exclusion criteria were as follows: if the paper was not about melasma, a repeat citation, retracted postpublication, animal studies, review articles, and meta-analysis. Eighty-nine articles remained after screening.

The results of the literature review and critical analysis are presented as five broad categories of interventions for melasma, which were informed and dictated by the results of the research. All studies

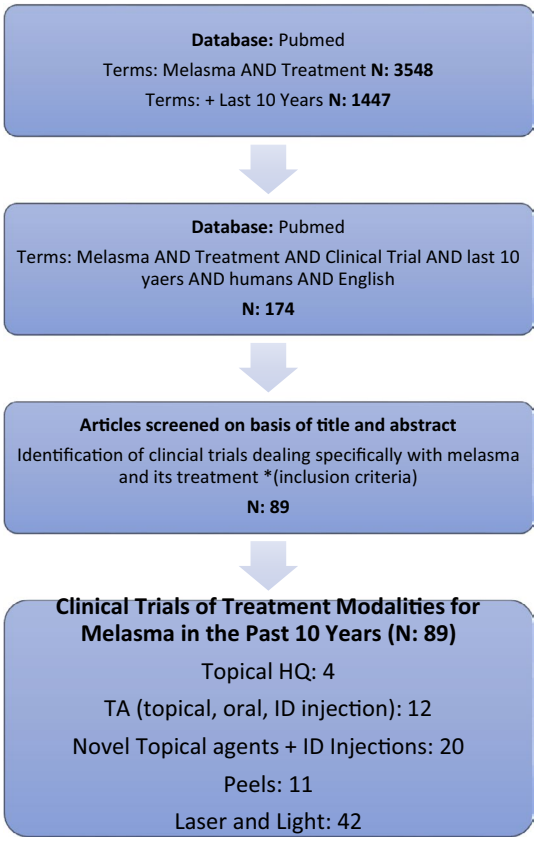

FIGURE 1 Flowchart depicting literature search

were included that met the criteria, providing a range of study types and levels of evidence.

The quality of the evidence presented in each individual study is rated using a modified scale derived from the Oxford Centre for Evidence-Based Medicine (Table 1).

4 | RESULTS

4.1 | Topical hydroquinone

Four studies were found evaluating the efficacy of hydroquinone 4% in the treatment of melasma (Table S1). Level 1 evidence was presented by Gong Z et al[10] who performed a randomized, placebo-controlled, double-blind study lasting 8 weeks in 233 Chinese patients comparing placebo to TCC and showed statistically significant improvement with the treatment cream.

Farshi[11] compared HQ 4% to AA 20% in a small prospective cohort study. MASI improved significantly with both treatments but surprisingly AA gave a better improvement than HQ. Though only representing level 2 evidence, this is relevant because it suggests that AA 20% may be a suitable alternative for patients who are not suitable for HQ; for example, during pregnancy, as well as a potential OTC replacement for HQ 4%.

Overall, these studies add more support to the efficacy as well as safety for HQ as first-line therapy for melasma. It is possible that adding AA 20% could work synergistically with HQ 4% but the increased irritation of the compounded product will be a limiting step in this treatment regime.

TABLE 1 Evidence quality rating scheme, modified from the Oxford centre for evidence-based Medicine for ratings of individual studies[9]

Level 1	Properly powered and conducted randomized clinical trial
Level 2	Well-designed controlled trial without randomization or prospective comparative cohort trial
Level 3	Case-control studies, retrospective cohort study
Level 4	Case series with or without intervention, cross-sectional study
Level 5	Opinion of respected authorities, case reports

4.2 | Tranexamic acid

In the past 10 years, 12 clinical trials were published examining the efficacy of TA in its various forms—oral, topical, and injectable (Table S2).

In a case series of 22 patients, Na[12] tried to elucidate a mechanism for the efficacy of both topical and oral TA when used together to treat melasma by examining skin biopsy specimens. They found that the treatment decreased epidermal pigmentation and also reversed the dermal changes seen in melasma. Though only representing level 4 evidence, this study is significant because it contributes to the understanding of both the pathophysiology and the mechanism of action of successful treatments. Facial skin biopsy studies are a clinical challenge and therefore not commonly undertaken so this paper is very helpful in helping to understand MOA at a cellular level.

Four studies specifically looked at the efficacy of PO TA dosed either at 250 mg BD or TDS. They all provide strong evidence that PO TA either dosed BD or TDS and combined with HQ 4% is very effective at improving melasma significantly over 12-16 weeks.

Though the safety of PO TA was not the primary focus of this literature review, it is noteworthy that none of the trials of PO TA reported any adverse events.

Overall, a number of high-quality studies support the use of TA in the treatment of melasma. Seven of the studies investigated the efficacy of PO TA, with a total of 585 subjects. Three of the 7 studies represented level 1 evidence (randomized, controlled, prospective, well-designed trials). PO TA was found to be effective as monotherapy as well as when combined with topical HQ, LFQS 1064 nm laser, and TCC regimen. The evidence suggests that the lightening effect of 250 mg BD dosing can be seen as early as 2 months into therapy. However, the risk of relapse remains high when TA is discontinued so perhaps TA therapy should be considered more of a long-term treatment. Though side effects are rare with PO TA, a DVT was reported in one patient taking it for melasma who was later found to have protein S deficiency. Therefore, clinicians should be vigilant about

screening patients for risk of thromboembolic disease, heart disease, and stroke when considering PO TA for melasma.[13]

4.3 | Novel oral, topical, and injectable treatments

Nineteen clinical trials were performed assessing various novel oral, injectable, and topical treatments for melasma (Table S3). New topicals include Lumixyl, an oligopeptide that inhibits tyrosinase[14]; cysteamine, an amino acid that inhibits melanogenesis in cell cultures[15,16]; and 75% mulberry extract oil.[17] The use of IL triamcinolone[18] and even acupuncture[19] was studied as well.

The majority of these studies have not been replicated and involve small patient numbers so no definitive conclusions can be drawn from them. However, they do highlight some new potential future treatments.

4.4 | Lasers and light

Twenty-three clinical trials were found investigating the role of the Q-switched Nd:YAG laser in the treatment of melasma (Table S4). Overall, the small sample size remains the major drawback of these studies, the largest sample size being 75 patients. Importantly, there have been no RCTs comparing the effectiveness of the Q-switched Nd:YAG laser (532 nm) to the standard topical treatments (TCC or HQ alone). Regardless, LFQS laser seems to at the moment be potentially one of the best options for treating melasma, especially in darker skin types. However, it is less effective as monotherapy and is best when combined with other lasers such as IPL, peels like glycolic peels and oral adjuvants such as TA.

In the past 10 years, 5 clinical trials have been published with the aim of providing evidence for the use of IPL in the treatment of melasma (Table S5). Overall, IPL only provides minimal improvement to melasma and any positive effect needs to be maintained post-treatment with topical therapy. There is a potential for using low-fluence or fractionated IPL to reduce the risk of aggravating pigmentation or causing PIH. IPL is best suited for Fitzpatrick skin types I-III due to the risk of PIH or hypopigmentation in those of darker skin types.

There have been 7 clinical trials of the use of nonablative fractional lasers in melasma (Table S6). Overall, the evidence suggests that the NAFL only bring about a mild to moderate improvement in melasma (if at all), with relapse occurring a few months post-treatment as well as a high incidence of PIH. Though they do appear to be relatively safe when low-fluence, nonaggressive protocols are used, the results are not superior to TCC, and there will still always be a risk of PIH. Based on the clinical trial evidence, the 1550 nm laser is not efficacious or safe for the treatment of melasma.

There were only two studies looking at the efficacy of fractional CO2 laser in the treatment of melasma, with a combined total of 70 patients so this type of laser cannot be recommended for the treatment of melasma (Table S7).

The first prospective clinical trial showing efficacy of the picosecond laser in the treatment of melasma was published in 2017 by Choi et al[20] (Table S8). This level 1 evidence, prospective, randomized, split-face, controlled trial of 78 patients with skin type IV compared the picosecond laser with HQ 2% to HQ 2% alone. The results were very encouraging: 76.92% of the combination treatment subjects had more than 51% improvement in mMASI score. Importantly, no adverse events occurred. However, the study was only 7 weeks long with no long-term follow-up so no comment can be made about longevity of results.

In 2018, there were two more high-quality clinical trials investigating the efficacy of the picosecond laser on melasma. However, both studies had very small sample sizes.[21]

The other study from 2018 was a split-face comparative study between the picosecond 755 nm laser and the Q-switched Nd:YAG. Only 12 subjects were studied over 16 weeks, skin types III and IV. Visual analogue scores were used to show that the picosecond laser provided faster and better clearance than the Nd:YAG. Again, the small sample size and lack of long-term follow-up proves problematic in recommending the picosecond laser for melisma.[22]

Though the picosecond laser appears very promising when combined with standard topical HQ therapy, as a fairly new modality, further studies are required to establish ideal settings and parameters for various skin types.

Three papers looked at the use of novel laser therapy in melasma 9 (Table S9). The use of pulsed dye lasers (PDLs) stems from recent advances in understanding that melasma has a vascular component.[1] In 2011, Passeron et al[23] performed a prospective, randomized, single-blind, split-face study comparing PDL and TCC in the form of Tri-Luma cream to TCC alone over 4 months. At 1-month post-treatment completion, a greater improvement was seen in the combined PDL and TCC group but only in the lighter skin type II and III patients.

In 2015, the use of a novel copper bromide laser was investigated in a randomized split-face clinical trial.[24] The copper bromide laser is composed 90% of yellow light (578 nm) and 10% of green light (511 nm). The yellow light preferentially targets vascular lesions while the green light targets pigment. The study compared the use of this laser with Kligman's solution to the laser in 20 patients with melasma (skin types II-IV). The topical treatment resulted in a greater decrease in MASI score than the laser treatment. Importantly, neither methods prevented relapse despite subjects wearing sunscreen daily. Also, this study suggests that the copper bromide laser did not effectively or efficiently target the vascular component of melasma.

Because of the risk of PIH in darker skin types with laser and light treatments, Shaikh and Mashood[25] investigated utilizing fluorescent pulsed light (FPL)—a form of IPL with a lower peak power and theoretically lower risk of PIH—with 5% topical magnesium ascorbyl phosphate (MAP)—a stable ester of ascorbic acid that functions as an antioxidant and inhibits melanogenesis. After 12 weeks of treatment, mean MASI scores were significantly reduced. However, there was gradual recurrence of melasma at 3 months post-treatment. However, this novel form of FPL combined with a topical agent did show promising results but maintenance therapy is most likely required.

4.5 | Peels

Twelve clinical trials were performed since 2009 investigating the effects of various peels on melasma (Table S10). Overall, peels have not been shown to be superior to the use of topical therapy alone. Additionally, when compared with topical monotherapy, peels are associated with both acute side effects of burning and discomfort as well as longer-term problems with PIH. SA peels are not effective in the treatment of melasma, unless potentially combined with mandelic acid. GA peels appear to be slightly more effective than TCA peels, and more efficacy can be gained when 5% MAP is added. However, GA peels are very irritating to patients—especially at very high strengths—and the research shows that AFA and 1% tretinoin peels are equally as effective but less irritating for patients.

5 | DISCUSSION

Based on literature review of evidence from the past 10 years, the following treatment ladder is proposed (Table 2):

Topical therapy with a HQ and retinoid-based product should be first line for a minimum of 3 months with the addition of oral tranexamic acid at 250 mg BD if no contraindication. Second-line treatment with lasers can then be added if available and financially feasible for the patient and, currently, the most reasonable first line is LFQS Nd:YAG. Though FDA-approved, fractional nonablative resurfacing was not effective as shown in the four clinical trials analyzed. The picosecond laser, as well as the pulsed dye laser in lighter skin types, is gathering a strong evidence base for their inclusion in the treatment ladder.

TABLE 2 Proposed therapeutic ladder for melasma based on literature review

First-line therapy	Control of risk factors (photoprotection, discontinue hormone treatments, or photosensitising medications) Topical anti-tyrosinase therapy combination, based on HQ 4% and tretinoin for 3 mo PO tranexamic acid 250 mg BD for 3 mo
Second-line therapy	Combination of first-line treatments + Laser treatment: LFQS Nd:Yag or Picosecond laser Skin types I/II/III: consider adjunctive therapy with PDL with setting aimed at vessels only
Third-line therapy	Combination of first-line treatments + a series of chemical peels (GA/TCA)

Third-line therapy would be the addition of chemical peels to the above treatments, with GA or TCA peels having the most evidence for effectiveness. However, of all the treatment modalities peels have the most short-term and long-term side effects for patients and therefore should only be considered as adjunct or third line.

In conclusion, there is a growing body of evidence for the efficacy of novel treatments for melasma, as well as new ways of optimizing existing treatments, that all clinicians faced with treating this skin condition should be familiar with, in order to provide patients with the best possible outcomes.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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