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EVIDENCE-BASED REVIEW

Treatment of Melasma with Topical Agents, Peels and Lasers: An Evidence-Based Review

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Abstract
Background Melasma is an acquired disorder of hyperpigmentation occurring on the face and predominantly affecting women of childbearing age. It is a chronic, often relapsing condition with a negative impact on quality of life. Current treatments for melasma are unsatisfactory.
Objective The aim of this article was to conduct an evidence-based review of interventions available for the treatment of melasma.
Methods A systematic literature search was performed using PubMed and the keywords 'melasma' or 'chloasma' in the title. The search was further refined by using a filter for 'controlled clinical trials' and 'randomized controlled trial'. The included studies were used to develop recommendations for treatment.
Results The electronic search yielded a total of 80 citations. Forty studies were included in this review, which had a total of 2,912 participants. Three different therapeutic modalities were investigated—topical agents, chemical peels, and laser and light therapies. Topical depigmenting agents were found to be the most effective in treating moderate-to-severe melasma, with combination therapies, such as triple-combination therapy (hydroquinone, tretinoin, and fluocinolone acetonide), yielding the best results. Chemical peels as well as laser and light therapies were found to have moderate benefit but more studies are needed to determine their efficacy and long-term safety. Adverse events associated with treatment were mild and short-lasting and included skin irritation, dryness, burning, and erythema. The data could not be statistically pooled because of the heterogeneity of treatments and lack of consistency across study designs.
Conclusions Topical combination therapies were found to be more effective than monotherapy. Triple combination therapy was found to be the most effective, but approximately 40 % of patients develop erythema and peeling. Chemical peels and laser and light therapies produced mixed results, with increased risk of irritation and subsequent hyperpigmentation, particularly in darker-skinned individuals. Hence, current treatments available for melasma remain unsatisfactory. Many of the studies lacked long-term follow-up. Limitations of current literature include the heterogeneity of study designs, small sample sizes, and poor follow-up rates. Additional evidence for the effects and role of sunscreens is needed. Categorization or stratification of demographic data should also be included in future studies, such as age, melasma type, and duration of melasma prior to initiation of treatment. Patient's perception of improvement versus investigator's assessment of improvement should also be included in future studies and standardized methods of study design and assessment of outcomes are needed to form definitive conclusions on the efficacy of different treatment modalities.

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1 Background

1.1 Etiology

Melasma is an acquired disorder of the skin characterized by bilateral, hyperpigmented, irregularly shaped macules on the face that predominantly affects women. Melasma

tends to be prevalent in patients with darker skin types and serves as a cause of significant psychological distress in affected patients [1]. Despite numerous studies on melasma, the etiology of this disorder remains unknown. However, there is strong evidence implicating sex hormones and sun exposure as potential triggers or causes [2–4]. Melasma occurs primarily in women of childbearing age, particularly during pregnancy or with use of oral contraceptives, but an exact mechanism involving hormones has not yet been elucidated [3]. Increased sun exposure and genetics have been shown to play a role as well, as evidenced by its tendency to run in families and its higher prevalence in countries around the equator [5]. Although uncommon, melasma may also occur in men.

1.2 Clinical Features

Melasma is diagnosed clinically based on the presence of hyperpigmented macules on the malar regions, forehead, upper lip and mandible. Three clinical types of melasma exist: centrofacial, malar and mandibular, based on distribution. Melasma is also classified by the degree of melanin deposition in the skin: epidermal, dermal and mixed melasma. Epidermal melasma is the most common and is characterized by increased melanin in the epidermis; dermal melasma is characterized by increased melanin in the dermis, whereas mixed refers to a combination of epidermal and dermal melasma [6]. A Wood's lamp examination allows for distinction between the melasma types; however, dermal melanin is often found histologically in patients with Wood's lamp-diagnosed epidermal melasma. Melasma can last for years and is often recalcitrant to treatment. Melasma associated with pregnancy may persist for months after delivery and after cessation of oral contraceptives [3]. Melasma has been shown to worsen with sun exposure, even after successful treatment. [6]

1.3 Interventions

A range of treatments for melasma exist, with varying degrees of efficacy and success. These include depigmenting agents, topical retinoids, topical steroids, peeling agents, laser and light therapies, combination therapies, and other less-studied modalities. Long-term treatment and prevention has been difficult to achieve and adverse effects such as skin irritation, peeling, burning, stinging, and post-inflammatory hyperpigmentation are common.

2 Objective

The aim of this review was to determine the effectiveness of available treatments for melasma and to identify the limitations in the current literature as well as the need for future areas of research. Currently, the treatments available for melasma are unsatisfactory and some carry the risk of producing mild to severe side effects such as irritation and post-inflammatory hyperpigmentation, particularly in darker skin types.

3 Methods

A PubMed (National Library of Medicine) search was conducted using the keywords 'melasma' and 'chloasma' in the title. Additionally, a filter for 'controlled clinical trials' and 'randomized controlled trial' was used. Studies included were limited to prospective, randomized controlled clinical trials evaluating the treatment of melasma. The Cochrane database was also used to search for published systematic reviews. Studies not available in English were excluded. Trials included in larger, multi-trial studies that were already included in the review were also excluded. Studies with patients having other pigmentary disorders and studies with oral or systemic treatments were excluded. No year limits were applied to the searches and there were no restrictions on age, ethnicity, or skin types of patients. Only completed trials were included. Publications were included through March 2013. The outcomes that were measured included physician- and participant-assessed response to treatment, objective measurements of melasma treatment outcome, time elapsed before clinical improvement, and adverse events.

4 Results

4.1 General

The electronic search yielded a total of 80 citations (Fig. 1). A total of 40 studies, which fit the inclusion criteria, were included in this review. The total sample size was 2,912. The number of participants in each study ranged from 10 to 641, and the duration of the studies ranged from 4 weeks to 12 months. Studies were obtained from several different countries. Of the studies reviewed, 14 were placebo-controlled studies, 26 studies compared interventions, and 19 were split-face studies. One systematic review was obtained from the Cochrane database [7]. Interventions included depigmenting agents such as hydroquinone and azelaic acid, retinoid topical therapies, chemical peels, laser and light therapies, as well as combinations of different treatment modalities.

Results for the studies reviewed are included in Tables 1, 2, 3, and 4. They have been divided into four categories: studies evaluating topical agents as monotherapy for the treatment of melasma; studies evaluating

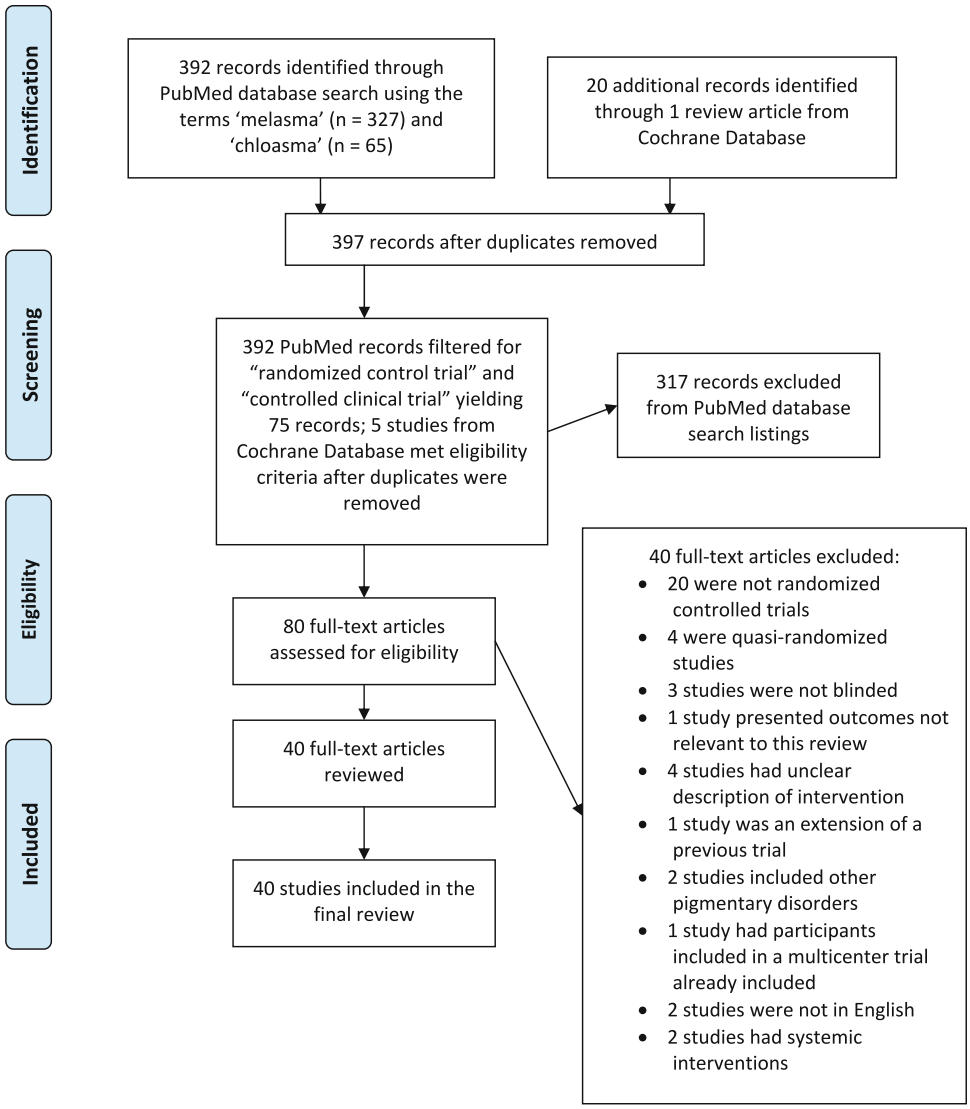

Fig. 1 Article selection flow diagram

more than one or a combination of topical agents; studies evaluating chemical peels as monotherapy, in conjunction with or versus other therapies; and studies evaluating laser and light as monotherapy, in conjunction with or versus other therapies. The large degree of variation in the designs of the studies precluded the use of statistical analysis between studies with similar interventions. The endpoints used were the physician- and participant-assessed outcomes of melasma treatment, objective measurements of melasma treatment outcomes, time elapsed before clinical improvement was observed, and adverse events.

4.2 Topical Agents

4.2.1 Depigmenting Agents

Depigmenting agents have been the gold standard for the treatment of melasma for decades (Table 1). Hydroquinone has been the most extensively studied depigmenting compound for the treatment of melasma. The mechanism of action of hydroquinone is via inhibition of tyrosinase, an enzyme critical to the pigment-producing pathway in melanocytes. One of the earliest studies investigating the efficacy of hydroquinone for the treatment of melasma in which the MASI (Melasma Area and Severity Index) score was used as an outcome measure was conducted by Ennes et al. [8] who compared 4 % hydroquinone to placebo in a 12-week study. They found that 38 % of patients in the hydroquinone group achieved complete clinical response versus only 8 % in the placebo-treated group, with clinical improvement observed within 3 weeks of treatment. A separate study conducted by Vázquez and Sánchez [9] examining the effects of sunscreen on the efficacy of hydroquinone found that the addition of sunscreen to hydroquinone led to greater improvement of melasma (96.2 %) when compared with the use of hydroquinone

Table 1 Studies evaluating topical agents as monotherapy for the treatment of melasma

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Vázquez and Sánchez, 1983 [9]	Randomized, double-blind, placebo-controlled	3 % hydroquinone twice daily and placebo cream vs. 3 % hydroquinone and broad spectrum sunscreen for 12 weeks	53	Physician-assessed improvement noted in 96.2 % of participants using sunscreen vs. 80.7 % using placebo	Subjective evaluation by investigators and participants. Sunscreen SPF not specified
Baliña and Graupe, 1991 [10]	Randomized, double-blind, multicenter	4 % hydroquinone cream applied to face twice daily vs. 20 % azelaic acid cream applied twice daily for 24 weeks; daily sunscreen application in both groups	243	Azelaic acid produced 'good' or 'excellent' results in 65 % of subjects vs. 72 % of subjects in hydroquinone group; no significant difference between groups	SPF of sunscreen or application frequency not specified; no participant assessments of treatment response
Griffiths et al., 1993 [21]	Randomized, double-blind, vehicle-controlled	0.1 % tretinoin vs. vehicle cream once daily to face for 40 weeks; SPF 15 sunscreen used in both groups	38	68 % in tretinoin group 'improved' or 'much improved' vs. 5 % in vehicle group based on physician evaluation; colorimetry and histological examination of lesions correlated with clinical assessment	Significant improvement occurred after 24 weeks of tretinoin treatment; erythema and desquamation observed in 88 % of tretinoin-treated subjects; all subjects were Caucasian. No participant assessment of treatment response
Kimbrough-Green et al., 1994 [22]	Randomized, double-blind, vehicle-controlled	0.1 % tretinoin vs. vehicle cream once daily to face for 40 weeks; sunscreen SPF 15 sunscreen used in both groups	28	32 % improvement in MASI score in tretinoin-treated group vs. 10 % improvement in the vehicle group; colorimetry and histological examination of lesions correlated with physician clinical assessment	Significant improvement occurred after 24 weeks of tretinoin treatment; erythema and desquamation observed in the majority of tretinoin-treated subjects (67 %); all subjects were African American. No participant assessment of treatment response
Sivayathorn et al., 1995 [11]	Randomized, double-blind, multicenter	2 % hydroquinone cream twice daily vs. 20 % azelaic acid cream twice daily for 24 weeks; broad spectrum sunscreen used by both groups	300	68.9 % of participants in azelaic acid group reported 'good' or 'excellent results' vs. 43.7 % in the hydroquinone group (statistically significant). Overall improvement rating assessed by physicians	Rate of adverse effects was 36.5 % in azelaic acid group vs. 12.7 % in hydroquinone group. Adverse effects were mild and transient. SPF of sunscreen and daily use not specified. No participant assessment of treatment response
Leenutaphong et al., 1999 [23]	Randomized, double-blind, vehicle-controlled	0.05 % isotretinoin gel vs. vehicle cream twice daily for 40 weeks; daily SPF 28 sunscreen used in both groups	23	MASI score decreased 68.2 % in isotretinoin group vs. 60 % in vehicle group; colorimetry showed 47 % decrease in isotretinoin group vs. 34 % decrease in vehicle group; However, no statistically significant difference in outcomes between groups	Mild and transient dermatitis in 27 % of isotretinoin-treated group vs. 0 % in the vehicle group
Ennes et al., 2000 [8]	Randomized, double-bind, placebo-controlled	4 % hydroquinone and two sunscreens (SPF 15) twice daily vs. cream containing two sunscreens (SPF 15) twice daily for 12 weeks; daily morning application of SPF 30 sunscreen in both groups	45	38 % in the hydroquinone group showed complete resolution of melasma vs. 8 % in placebo group	Physician subjective evaluation using non-validated scale; adverse effects included mild irritation and erythema. No participant assessment of treatment response. No difference in tolerability

Table 1 continued

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Huh et al., 2003 [14]	Randomized, double-blind, placebo-controlled, split-face	Vitamin C iontophoresis applied for 8 min twice a week to one side of face for 12 weeks vs. distilled water iontophoresis applied for 8 min twice a week to other side of face for 12 weeks; daily sunscreen used in both groups	29	Colorimetry found significant decrease in luminance value from 4.60 to 2.78 in vitamin C-treated side vs. decrease in *L* value from 4.45 to 3.87 in control side	SPF of sunscreen not specified
Francisco-Diaz et al., 2004 [18]	Randomized, double-blind, placebo-controlled, split-face	Gigawhite® 5 % solution twice daily for 12 weeks vs. placebo solution twice daily for 12 weeks; both groups used daily SPF 60 sunscreen	26	MASI decreased by 18.5 % on Gigawhite® side vs. 13.5 % on placebo side, with no significant difference. No significant difference noted on subjective measures. Significant difference noted on colorimetry with 6.9 % in luminance on Gigawhite® side vs. 1.03 % on placebo side	No adverse effects reported
Thirion et al., 2006 [17]	Randomized, double-blind, placebo-controlled	Thiospot® intensive cream vs. moisturizing cream applied twice daily to forehead for 3 months	27	Significant difference found using mexameter, video-recorded ultraviolet light reflection, corneomelametry, and physician subjective assessment with Thiospot® group vs. moisturizing cream	Investigators limited inclusion to forehead melasma only. Unclear if there was exclusion for melasma elsewhere (e.g. chin, cheeks). No adverse effects reported. Sunscreen use was not reported
Khemis et al., 2007 [15]	Randomized, double-blind, vehicle-controlled, split-face	Phase 1: rucinol serum 0.3 % vs. vehicle applied to the face twice daily for 12 weeks; Phase 2: subjects treated with additional 3 months of full-face rucinol treatment with assessments at 16, 20, and 24 weeks. Daily SPF 60 sunscreen used in both groups	28 completed phase 1; 26 completed phase 2	Phase 1: pigmentation score of rucinol-treated side was significantly lower than vehicle-treated side Phase 2: pigmentation score showed significant reduction in previously rucinol-treated side; colorimetry showed significant decrease in pigmentation in rucinol-treated side	Treatment response was assessed with a pigmentation scale designed by the investigators Tolerability was high (78 %) as rated by participants Reduced adverse effects on rucinol-treated side when compared with vehicle-treated side
Huh et al., 2010 [16]	Randomized, double-blind, vehicle-controlled, split-face	Liposome-encapsulated 4-*n*-butylresorcinol 0.1 % cream applied to one side of face twice daily, vehicle applied to the other side of face twice daily for 8 weeks	23	Significant reduction in melanin index of the 4-*n*-butylresorcinol-treated side when compared with vehicle-treated side	No adverse effects reported More than 60 % of participants considered treatment efficacious after 8 weeks
Alvin et al., 2011 [26]	Randomized, single-blind, placebo-controlled	75 % mulberry extract oil applied to the face vs. placebo daily and assessed at 4 and 8 weeks	50	MASI scores and mexameter scores decreased at 8 weeks from baseline in the mulberry extract group when compared with the placebo group. Decrease was statistically significant	Adverse effects were minimal, with mild pruritus observed in fewer subjects in the 75 % mulberry extract oil group (4) vs. placebo group (12). Improvement in MELASQOL score was also noted in the intervention group vs. the placebo group

Table 1 continued

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Kanechorn et al., 2012 [24]	Randomized, double-blind, vehicle-controlled, split-face	Topical 5 % tranexamic acid applied to one side of face twice daily vs. vehicle applied to other side of face daily for 12 weeks; sunscreen used twice daily in both groups	21	MASI score and melanin index were reduced on both sides of face at 12 weeks when compared with baseline. No significant difference found between the intervention and vehicle groups	Significant increase in erythema observed in the tranexamic acid-applied side of the face
Altaei, 2012 [27]	Randomized, double-blind, placebo-controlled	Group 1 (silymarin cream 7 mg/ml) vs. Group 2 (silymarin cream 14 mg/mL) vs. Group 3 placebo applied to face twice daily for 4 weeks; SPF 15 sunscreen used daily in all groups	96	MASI score reductions in silymarin-treated groups were statistically significant beginning in the first week. Patient satisfaction was recorded at 100 % in the silymarin-treated groups	No local or systemic adverse effects were reported

Gigawhite® tyrosinase inhibitor made from plant extracts (Pentapharm/DSM, Basel, Switzerland), *MASI* Melasma Area and Severity Index, *MELASQOL* Melasma Quality of Life Scale, *SPF* sun protection factor, *Thiospot*® intensive cream contains thioctic acid, ethyl linoleate, octadecenedioic acid, lactic acid, UVB filter (Synchroline, Salo, Italy)

alone (80.7 %). While these findings were based on subjective assessment by investigators, clinical practice today supports the use of sunscreen in the treatment of melasma. This study also helped to establish the efficacy of hydroquinone as a depigmenting agent for melasma.

Another depigmenting agent, azelaic acid, has gained attention as an alternative to hydroquinone in the treatment of melasma. In 1991, Baliña and Graupe [10] compared 4 % hydroquinone with 20 % azelaic acid in the treatment of melasma in patients. While no statistical significance in physician assessment was noted between the two groups, 72 % of participants in the hydroquinone group reported a good to excellent response, while 65 % reported the same in the azelaic acid group. In a study carried out by Sivayathorn and colleagues [11] in Thailand comparing a lower concentration of hydroquinone (2 %) with 20 % azelaic acid, they found that 68.9 % of participants in the azelaic acid group achieved good or excellent response versus 43.7 % in the 2 % hydroquinone group. No significant improvement in lesion size was found between groups, and azelaic acid was associated with a greater rate of adverse effects (36.5 %) when compared with the hydroquinone-treated group (12.7 %). In both studies, the use of azelaic acid was associated with more adverse effects than with hydroquinone. In a more recent study conducted by Farshi [12] comparing the efficacy of 20 % azelaic acid with 4 % hydroquinone in two groups of women with melasma, a statistically significant difference was found between both groups after 2 months of treatment, with azelaic acid showing a greater decrease in MASI score (3.8 ± 2.8 vs. 6.2 ± 3.6 in the hydroquinone group). However, follow-up data beyond the 8 weeks of treatment was not available and no objective measure of treatment outcome was used.

Ascorbic acid or vitamin C has also been studied in the treatment of melasma. Ascorbic acid is believed to have depigmenting properties via its ability to chelate copper ions used in cellular enzymatic steps required for pigmentation. In a split-face, randomized controlled trial conducted by Espinal-Perez and colleagues [13] comparing 5 % L-ascorbic acid with 4 % hydroquinone, colorimetric analysis revealed no significant difference between the groups, and only slight improvement using physician subjective evaluation, with irritation reported in participants treated with hydroquinone. Similarly, Huh and colleagues [14] also examined the role of vitamin C in the treatment of melasma but instead compared vitamin C iontophoresis with distilled water iontophoresis in a split-face study. Colorimetry found a significant decrease in the luminance (L) value in the vitamin C-treated side (4.60 to 2.78) versus the control side (4.45 to 3.87).

Another compound that has recently been studied for its potential in treating melasma is rucinol serum, an agent

with depigmenting effects via tyrosinase inhibition. Khemis et al. [15] studied the efficacy of rucinol versus vehicle in a 12-week split-face trial for the treatment of melasma. They found that the rucinol-treated side had significantly less pigmentation, as measured by a pigmentation scale designed by the investigators. Additionally, colorimetry showed a significant decrease in pigmentation in the rucinol-treated side as well, and tolerability was deemed 'good' by participants. In testing the same compound with a different name, Huh and colleagues [16] conducted a split-face trial to evaluate the efficacy and safety of liposome-encapsulated 4-*n*-butylresorcinol 0.1 % cream and found it to significantly decrease pigmentation using mexameter measurements after 8 weeks, when compared with the vehicle group, and was also well tolerated.

Commercially prepared depigmenting agents for the treatment of melasma have become very popular worldwide. One such product whose efficacy and safety has been tested in a randomized clinical trial has been Thiospot® intensive, a Belgian cosmetic-whitening formulation believed to have tyrosinase-inhibiting properties. It is a formulation containing ethyl linoleate, thioctic acid, octadecanedioic acid, lactic acid, and ethylhexyl methoxycinnamate. In this trial, Thirion et al. [17] compared this formulation to a moisturizing cream for the treatment of melasma with twice-daily application for 3 months to the forehead and found a significant difference between the groups using mexameter, video-recorded ultraviolet light reflection, corneomelametry, and physician subjective assessment, with improvement seen across all parameters in participants treated with Thiospot®. Investigators of this study limited treatment to forehead melasma.

Another commercially developed whitening agent that has been studied in the treatment of melasma is 5 % Gigawhite®, a compound created with plant extracts and believed to have tyrosinase-inhibiting properties. In a 12-week, split-face study, Francisco-Diaz and colleagues [18] found a statistically significant difference using colorimetry in comparing both sides of the face, with 6.9 % improvement on luminance (L^* value) on the Gigawhite®-treated side compared with 1.03 % on the placebo-treated side. No significant difference was found in MASI scores between both groups and no adverse effects were reported.

4.2.2 Retinoid Therapies

Retinoid therapy has been used as monotherapy for melasma with moderate efficacy. Retinoids are believed to lighten hyperpigmented skin by decreasing melanosome transfer, inhibiting tyrosinase transcription, and interrupting the synthesis of melanin [19, 20].

In comparing the use of 0.1 % tretinoin cream with placebo in a 40-week study of Caucasian women with melasma, Griffiths et al. [21] showed that 68 % of participants in the tretinoin group had improvement of their melasma compared with only 5 % in the vehicle group. An average of 24 weeks lapsed in order for any significant clinical improvement to be observed, with a majority (88 %) of participants reporting adverse effects such as erythema and desquamation. In a similarly designed study, Kimbrough-Green et al. [22] sought to investigate the efficacy of tretinoin in African American subjects. In this study, it was found that there was an improvement of melasma in the tretinoin group with a MASI score decrease by 32 % versus only a 10 % decrease in the placebo group. As in the study by Griffiths et al. [21], it also took 24 weeks before any clinical improvement was noticed. In both studies, colorimetry and histological findings before and after treatment correlated with physician clinical assessment.

Leenutaphong et al. [23] investigated the use of 0.05 % isotretinoin gel versus placebo in Thai patients with melasma and found that there was no statistically significant difference in MASI scores and colorimetry between the two groups after 40 weeks. A transient and mild dermatitis was observed in nearly one-third of patients in the isotretinoin group.

4.2.3 Other Topical Therapies

Tranexamic acid has recently been studied as a potential new topical treatment for melasma but thus far studies have yielded disappointing results. In a split-face trial conducted by Kanechorn et al. [24] no significant difference was found between placebo and tranexamic acid, which is believed to inhibit the melanin production pathway via plasmin and plasminogen binding. There was a statistically significant decrease in MASI scores found at 12 weeks when compared to baseline; however, this could be attributed to the use of daily sunscreen, which more than half of the study participants reported rarely using prior to participation in the trial. In addition, the side treated with tranexamic acid showed more adverse effects than the placebo-treated side.

Lee and colleagues [25] sought to investigate clinical efficacy in the treatment of melasma using topical application of 2 % lincomycin and 2 % linoleic acid in combination with 0.05 % betamethasone valerate. They found that after 6 weeks, the average MASI score of the group treated with lincomycin, linoleic acid and betamethasone valerate decreased by 31.1 %, compared with 2 % in the vehicle group and 14.6 % in the group treated with lincomycin and betamethasone valerate alone. Linoleic acid is believed to have skin-lightening effects through inhibition of melanogenesis by increasing proteolytic degradation of tyrosinase and increasing stratum corneum turnover [23].

Table 2 Studies evaluating more than one or a combination of topical agents for the treatment of melasma

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Lim, 1999 [32]	Randomized, split-face	2 % kojic acid in a gel containing 10 % glycolic acid and 2 % hydroquinone applied to one half of the face twice daily vs. gel containing only 10 % glycolic acid and 2 % hydroquinone to the other half of face twice daily for 12 weeks; SPF 15 sunscreen used daily	40	In 60 % of patients in the kojic acid group, more than 50 % of melasma cleared vs. 47.5 % of those in the 10 % glycolic acid and 2 % hydroquinone group	Mild adverse effects noted in both groups were transient; complete clearance of melasma occurred in two patients in the kojic acid group; subjective measurement of improvement
Lee et al., 2002 [25]	Randomized, double-blind	Vehicle (Group A) vs. 2 % lincomycin mixed with 0.05 % betamethasone valerate (Group B) vs. 2 % lincomycin mixed with 0.05 % betamethasone valerate and 2 % linoleic acid (Group C) applied nightly on the face for 6 weeks. Daily SPF 15 sunscreen use	47	MASI score of Group C decreased by 31.1 %, compared with only 2 % in Group A, and 14.6 % in Group B. There was no statistically significant difference between Group A and Group B. 43.7 % of patients in Group C had more than moderate improvement in objective assessment, compared with none in Group A and 12.5 % in Group B	Sunscreen frequency of application was unclear
Guevara and Pandya, 2003 [31]	Randomized, double-bind, vehicle-controlled	4 % hydroquinone, 10 % buffered glycolic acid, vitamin C and E, sunscreen cream twice daily for 12 weeks vs. sunscreen twice daily for 12 weeks	35	Mexameter results showed significant difference in reduction of pigmentation. 75 % of those in the study cream group vs. 13 % in the sunscreen group showed improvement	SPF of study cream unknown
Taylor et al., 2003 [28]	Randomized, investigator-blinded	TC (hydroquinone 4 %, tretinoin 0.05 %, fluocinolone acetonide 0.01 %) daily vs. dual combinations of above ingredients daily for 8 weeks	641	26.1 % of subjects treated with TC achieved complete clearance vs. maximum of 4.6 % in other groups. In over 70 % of subjects treated with TC 75 % or more improvement noted vs. only 30 % in patients with other dual combination groups	Improvement based on physician subjective evaluation; adverse effects such as erythema, stinging and burning were significant and noted in all groups and were transient and mild
Espinal-Perez et al., 2004 [13]	Randomized, double-blind, split-face	5 % L-ascorbic acid applied to one side of face vs. 4 % hydroquinone applied to the other half of face for 16 weeks; sunscreen used every morning	16	Subjective participant assessment rated 93 % improvement as 'good' or 'excellent' on hydroquinone side vs. 62.5 % on ascorbic acid side. Colorimetry showed no statistical significance	More adverse effects seen in hydroquinone side (68.7 %) vs. ascorbic acid side (6.2 %); SPF of sunscreen used by participants unknown
Chan et al., 2008 [29]	Randomized, investigator-blinded	TC (hydroquinone 4 %, tretinoin 0.05 %, fluocinolone acetonide 0.01 %) at bedtime for 8 weeks vs. hydroquinone 4 % cream twice daily for 8 weeks	260	Melasma global severity score revealed mild or no melasma in 64.2 % of participants in the TC group vs. 39.4 % in the hydroquinone group. Participant assessment showed 70.8 % satisfaction in the TC group vs. 49.6 % in the hydroquinone group	Improvement measured subjectively by both participants and investigators; adverse effects observed mainly in the TC group but tended to be mild and transient

Table 2 continued

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Arellano et al., 2012 [30]	Randomized, investigator-blinded	6-month maintenance therapy with TC therapy (hydroquinone 4 %, tretinoin 0.05 %, fluocinolone acetonide 0.01 %) following 8 weeks of daily TC application; subjects randomized to twice weekly TC vs. tapering regimen [3 ×/week (first month), 2/week (second month), 1/week (fourth month)]	242	No relapse in melasma observed in 53 % of participants; twice-weekly TC group had lower relapse rate compared with the tapering regimen group	Mean time for relapse was 190 days for both groups; no serious adverse effects reported
Farshi, 2011 [12]	Randomized, open-label	4 % hydroquinone twice daily vs. 20 % azelaic acid twice daily for 8 weeks; broad-spectrum sunscreen used by both groups	29	Significant difference in MASI scores between both groups observed after 8 weeks, with the azelaic acid group having a lower MASI score	No objective measures for treatment used; SPF of sunscreen and frequency of application was not specified

MASI Melasma Area and Severity Index, *SPF* sun protection factor, *TC* triple combination cream

Alternative treatments for melasma have also included natural extracts, which may contain depigmenting compounds. In an 8-week study, Alvin et al. [26] compared the efficacy of an antioxidant, 75 % mulberry extract oil, with placebo, with a statistically significant decrease noted in both MASI score and mexameter readings by the 8th week. Quality-of-life measurement using MELASQOL (Melasma Quality of Life Scale) scores showed improvement in patients treated with the extract, and few adverse events were reported. In a 4-week study, Altaei [27] showed that silymarin, a natural polyphenolic flavonoid with potent antioxidant properties, was effective in the treatment of melasma in Iraqi patients. MASI score reductions in the silymarin-treated groups were statistically significant, beginning in the first week of treatment, when compared with placebo, and a 100 % patient satisfaction rate was recorded in the silymarin-treated groups.

4.2.4 Combination Creams

Triple combination therapy, comprised of hydroquinone, a retinoid and a fluorinated steroid, is considered to be a highly effective and safe treatment for melasma (Table 2). Derived from the Kligman-Willis formula, it has been modified and most recently used as a combination of 4 % hydroquinone, 0.05 % tretinoin and 0.01 % fluocinolone acetonide. One of the earliest studies showing the high efficacy of triple combination therapy was that conducted by Taylor et al. [28] comparing triple-combination cream with three dual-combination preparations (4 % hydroquinone + 0.05 % tretinoin, 0.05 % tretinoin + 0.01 % fluocinolone acetonide, and 4 % hydroquinone + 0.01 % fluocinolone acetonide) with nightly application for 8 weeks. Complete clearance was achieved in 26.1 % of participants using triple-combination cream, in comparison with 9.5 % using hydroquinone plus tretinoin, 1.9 % in tretinoin plus fluocinolone, and 2.5 % in hydroquinone plus fluocinolone. Additionally, complete or near complete clearance was achieved in 77 % of patients on the triple combination therapy versus a maximum of 46.8 % in subjects using the dual combination preparations. Adverse effects included erythema, peeling, irritation, and dryness, with the highest rates reported in the combination regimens containing tretinoin. Erythema and peeling were seen in approximately 40 % of patients on triple combination cream or dual combination cream containing tretinoin.

In a randomized clinical trial, Chan et al. [29] set out to investigate if triple combination therapy (hydroquinone 4 %, tretinoin 0.05 %, fluocinolone acetonide 0.01 %) was more effective than hydroquinone 4 % alone. They found that the triple combination therapy was more effective, with greater participant satisfaction being reported in the

triple combination group in comparison with the hydroquinone group.

Another study attempted to determine the maintenance therapy for patients in whom triple combination therapy had shown to be effective. Arellano et al. [30] showed that a twice-weekly application of triple combination therapy as maintenance was more effective in preventing melasma than a tapering regimen monthly from 1 to 4 months.

Other combination creams have been studied and have shown promising results. For example, a twice-daily application of a combination cream comprised of 4 % hydroquinone, 10 % buffered glycolic acid, vitamin C and E, and sunscreen showed a significant reduction in pigmentation when compared with twice-daily application of sunscreen alone in a study by Guevara and Pandya [31]. They showed a 75 % improvement in mexameter reading in the combination cream group versus only a 13 % improvement in the sunscreen-only group.

The efficacy of another combination preparation, 2 % kojic acid in a gel containing 10 % glycolic acid and 2 % hydroquinone, was investigated in a randomized, split-face study conducted by Lim [32]. The gel formulation was applied to one-half of the face twice daily and compared with a gel containing only 10 % glycolic acid and 2 % hydroquinone applied to the other half of the face twice daily for 12 weeks. It was discovered that in 60 % of patients in the kojic acid group, more than half of the melasma lesions had cleared versus only 47.5 % of those in the glycolic acid and hydroquinone group.

4.3 Chemical Peels

Chemical peels such as alpha hydroxyl acids and beta hydroxyl acids have been used for many years in the treatment of melasma, particularly in refractory cases. The results of studies comparing the efficacy of chemical peels have generally yielded mixed results (Table 3).

4.3.1 Glycolic Acid Peels

A split-face study conducted by Lim and Tham [33] compared two interventions: 2 % hydroquinone, 10 % glycolic acid gel twice daily, followed by 20–70 % glycolic acid peel every 3 weeks versus 2 % hydroquinone, 10 % glycolic acid gel twice daily alone for a total of 24 weeks. Although they found improvement in melasma in both groups, there was no significant difference between the two groups. One participant in the glycolic acid peel group reported the adverse effect of a painful burn with the treatment, with ensuing post-inflammatory hyperpigmentation for 2 months.

In a single-blinded, split-face study, Hurley et al. [34] showed that 20 % glycolic acid peels every 2 weeks did not enhance the efficacy of twice-daily application of 4 % hydroquinone treatment when compared with twice-daily 4 % hydroquinone monotherapy. Both groups in this trial showed improvement from baseline, but no significant difference in MASI scores between them.

In a separate, randomized, split-faced study conducted by Faghihi and colleagues [35] comparing 70 % glycolic acid peel versus 1 % tretinoin peel at 2-week intervals for four sessions, they found that there was a significant reduction in MASI scores for both groups from baseline to week 12 yet no significant difference in MASI scores between both groups. In addition, participants in the glycolic acid peel group reported lower tolerability to the intervention than participants in the tretinoin peel group. Similar results were found in a randomized, split-face trial comparing serial peels at 2-week intervals of glycolic acid versus serial peels at 2-week intervals of amino fruit acid [36]. The MASI scores of participants in this study at 3 and 6 months revealed a significant decrease from baseline in both groups but no difference in MASI scores between the two intervention groups.

4.3.2 Salicylic Acid Peels

The salicylic acid peel has also been used for the treatment of melasma. In a study conducted by Ejaz et al. [37] comparing Jessner's peel (14 % salicylic acid, 14 % lactic acid, 14 % resorcinol in alcohol) with a 30 % salicylic acid peel, they found no significant difference in MASI scores at 12 or 24 weeks between the two regimens, with significant reductions in MASI scores from baseline in both groups. There was also excessive crusting of the face noted in both groups.

In another study involving the application of salicylic acid peels, a randomized controlled, split-face study conducted by Kodali et al. [38] found that 20–30 % salicylic acid peels did not enhance efficacy of 4 % hydroquinone cream in the treatment of melasma, despite both groups showing significant reductions in pigmentation.

Another study comparing three interventions—Jessner's peel versus trichloracetic acid 20 % peel versus topical hydroquinone 2 % and kojic acid for 16 weeks—found that the MASI score for trichloracetic acid 20 % showed a greater reduction than Jessner's peel or topical hydroquinone 2 % with kojic acid at the 16-week follow-up visit [39]. However, post-inflammatory hyperpigmentation was more common in the chemical peel groups, with the trichloracetic acid peel group having a higher rate than the Jessner's peel group.

4.4 Laser Therapies and Light Therapies

Laser and light therapies for the treatment of melasma have become increasingly popular and have attracted greater

Table 3 Studies evaluating chemical peels as monotherapy, in conjunction with or versus other therapies for melasma

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Lim and Tham, 1997 [33]	Randomized, investigator-blinded, split-face	2 % hydroquinone, 10 % glycolic acid gel twice daily, followed by 20–70 % glycolic acid peel every 3 weeks for 24 weeks vs. pretreatment with 8 % glycolic acid cream twice daily for 2 weeks then 2 % hydroquinone, 10 % glycolic acid gel twice daily for 24 weeks; daily SPF 15 sunscreen use in both groups	10	Improvement of melasma and fine facial wrinkling observed on both sides; no statistically significant difference between the two groups	Frequency of sunscreen use not specified. Small sample size
Ejaz et al., 2008 [37]	Randomized, double-blind	Jessner's solution (14 % salicylic acid, 14 % lactic acid, 14 % resorcinol in alcohol) peel for 5 min every 2 weeks for 12 weeks vs. 30 % salicylic acid peel for 5 min every 2 weeks for 12 weeks; daily SPF 60 sunscreen use	60	Follow-up every 4 weeks up to 12 weeks after treatment stopped; no significant difference found between both groups. MASI scores dropped significantly following treatment in both groups	Moisturizer provided but sunscreen had to be purchased by participants; participants underwent 2 weeks of priming with 0.05 % tretinoin before treatment; adverse effects were mild and transient in both groups
Azzam et al., 2009 [39]	Randomized	Jessner's solution peel vs. trichloroacetic acid 20 % peel vs. topical hydroquinone 2 % and kojic acid 2 % for 16 weeks	45	MASI score after treatment found to be significantly lower in trichloracetic acid 20 % as compared with other groups	Post-inflammatory hyperpigmentation was more common with trichloracetic acid peel than with Jessner's solution
Ilknur et al., 2010 [36]	Randomized, single-blind, split-face	Twelve serial peels at 2-week intervals with glycolic acid vs. 12-week serial peels at 2-week intervals with amino fruit acid	24	MASI scores at 3 and 6 months revealed significant decrease in both groups; no difference between groups	Fewer side effects reported from amino fruit acid peels compared with glycolic acid peels, and found to be more tolerable
Kodali et al., 2010 [38]	Randomized, split-face	Four serial peels of 20–30 % salicylic acid every 2 weeks on one side of face with concomitant application of 4 % hydroquinone to both sides of face twice daily	18	Narrowband reflectance spectrophotometry showed significant reduction in pigment on both sides following treatment; no significant difference found between peeled and unpeeled sides	Participants were all Latin American women; small sample size
Faghihi et al., 2011 [35]	Randomized, double-blind, split-face	One side of face treated with glycolic acid 70 % peel vs. tretinoin 1 % peel on opposite side, each for four sessions at 2-week intervals	63	No significant difference between MASI scores in both groups; patients reported tretinoin 1 % peels more tolerable than glycolic acid 70 % peels	The use of sunscreen was not mentioned
Hurley et al., 2002 [34]	Randomized, investigator-blinded, split-face	4 % hydroquinone cream twice daily for 8 weeks vs. 4 % hydroquinone cream twice daily in addition to 20 % glycolic acid peels every 2 weeks for 4 weeks, followed by 30 % glycolic acid peels every 2 weeks for 4 weeks	18	Significant reduction in MASI score and mexameter results in both groups when compared with baseline; no significant difference found between groups	Participants were provided with moisturizers for use after hydroquinone application, as well as SPF 25 sunscreen to apply after hydroquinone cream. Small sample size

MASI Melasma Area and Severity Index, *SPF* sun protection factor

Table 4 Studies evaluating laser and light as monotherapy, in conjunction with or versus other therapies for melasma

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Wang et al., 2004 [40]	Randomized	4 % hydroquinone cream for 16 weeks vs. 4 % hydroquinone cream and IPL treatments every 4 weeks for four sessions (16 weeks); daily sunscreen use in both groups	31	39.8 % improvement in relative melanin index in the treatment group vs. 11.6 % improvement in the control group using hydroquinone only. 35 % in the treatment group had complete resolution vs. 14 % in the control group. At 24 weeks post-treatment, improvement in the IPL-treated group decreased to 24.2 %	Transient PIH noted in two patients in the treatment group. Frequency of hydroquinone application unclear; SPF of sunscreen and frequency not specified
Wattanakrai et al., 2010 [43]	Randomized, split-face	1,064 nm QS-Nd:YAG laser to half of the face for five sessions at 1-week intervals vs. 2 % hydroquinone applied to other half of the face. Study was 5 weeks long. SPF 60 used daily. Study had a 12-week post-treatment follow-up period	22	The laser side achieved an average 92.5 % improvement in relative lightness index and 75.9 % improvement in mMASI compared with 19.7 and 24 %, respectively, on the control side	Side effects were notable for mottled hypopigmentation, rebound hyperpigmentation. All patients had recurrence of melasma
Wind et al., 2010 [48]	Randomized, observer-blind, split-face	4–5 non-ablative 1,550 nm FLT sessions vs. daily TC (hydroquinone 5 %, tretinoin 0.05 %, triamcinolone acetonide 0.1 %) for 15 weeks; patients applied TC to both sides twice-weekly during follow-up	29	Worsening of hyperpigmentation was noticed on FLT side using mean PGA, PhGA, melanin index, and luminance value. No significant change observed on the TC side. Patients preferred TC at 6 months follow-up	FLT led to considerable side effects, including burning, stinging, erythema. PIH seen in 31 % of participants in the FLT group after two or more laser sessions
Kroon et al., 2011 [49]	Randomized, observer blind, split-face	Four serial non-ablative 1,550 nm FLT sessions at 2-week intervals vs. TC (hydroquinone 5 %, tretinoin 0.05 %, and triamcinolone acetonide 0.1 %) once daily for 8 weeks	22	PhGA improved at 3 weeks but no difference existed between both groups. At 6 months, melasma recurred in five patients in both groups. Participant satisfaction higher in the laser group vs. the TC group	Small sample size
Goldman et al., 2011 [41]	Randomized, split-face	TC applied to one side of the face with IPL sessions at 2 and 6 weeks vs. placebo cream applied to the opposite side of the face with IPL sessions at 2 and 6 weeks. Study was 10 weeks long	56	Using IGA, at week 10, 57 % of patients in the TC group were clear or almost clear compared with 23 % in the inactive cream group	Assessments were subjectively made by investigators
Passeron et al., 2011 [46]	Randomized, single-blinded, split-face	TC (hydroquinone 4 %, tretinoin 0.05 %, and fluocinolone acetonide 0.01 %) once daily plus three PDL serial sessions to one side of the face every 3 weeks after 1 month of starting TC; sunscreen with an SPF of at least 50 used daily	18	Significant decrease in MASI score in the TC plus PDL group at the end of treatment and after one summer (several months after study was completed) vs. TC-alone group	Unclear if sunscreen provided to patients; PIH observed in three patients on PDL side. This is the first time that a treatment has been shown to prevent relapse of melasma

Table 4 continued

Study, year	Study design	Treatment	No. of subjects	Outcome(s)	Comments
Park et al., 2011 [44]	Randomized, observer-blinded, split-face	1,064 nm QS-Nd:YAG for six sessions at 1–2 week intervals to the entire face plus 30 % glycolic acid peels for three sessions at 2-week intervals to one side of the face (6 weeks). Follow-up at 5 months post-treatment	16	The side with QS-Nd:YAG and glycolic acid peels showed an average 32.6 % improvement in mexameter readings and 37.4 % improvement in mMASI, compared with 22 % and 16.7 %, respectively, on the side treated with laser only. Subjective assessments by physicians and participants correlated with mMASI and mexameter findings	Sunscreen use not discussed Adverse effects included transient burning and mild edema
Hong et al., 2012 [47]	Randomized, split-face	Single-session of 1,550-nm FLT on one half of the face vs. 5 % trichloracetic acid peel on the other half of the face for 12 weeks	18	At 4 weeks follow-up, significant improvement observed in both groups. At 12 weeks, high recurrence rate observed. No statistical difference between both groups on MASI or participant assessment	Sunscreen use was not mentioned
Kar et al., 2012 [45]	Randomized	Group A: low fluence QS-Nd:YAG at weekly intervals vs. Group B: glycolic acid peel at 2-week intervals vs. Group C: high fluence QS-Nd:YAG at 2-week intervals; treatment duration was 12 weeks, with 12-week follow-up period	60	MASI score demonstrated statistically significant improvement with low-fluence QS-Nd:YAG compared to high fluence QS-Nd:YAG and glycolic acid peels	MASI scores rose in all three groups at the 12-week follow-up visit. Most adverse effects were seen in high fluence QS-Nd:YAG, which included mottled confetti-like hypopigmentation. Fewest adverse effects observed in the low fluence QS-Nd:YAG group
Figueiredo and Trancoso, 2012 [42]	Randomized, single-blinded, open-label	IPL and TC vs. TC alone, followed up at 6 and 12 months	62	MASI in the IPL group showed a 49.4 % reduction at 6 months and a 44.9 % reduction at 12 months from baseline In the control group, MASI did not decrease from baseline to 6 months	Investigators used own scale; duration of IPL not included, frequency of TC application not specified. Crusting and hyperpigmentation in the IPL group, with resolution within 2 weeks

FLT fractional laser therapy, *IGA* Investigator's Global Assessment, *IPL* intense pulsed light, *MASI* Melasma Area and Severity Index, *mMASI* modified MASI, *PDL* pulsed dye laser, *PGA* Patient Global Assessment, *PhGA* Physician's Global Assessment, *PIH* post-inflammatory hyperpigmentation, *QS-Nd:YAG* Q-switched neodymium-doped yttrium aluminum garnet, *SPF* sun protection factor, *TC* triple combination cream

interest in recent times. Like chemical peels, laser and light therapies carry an increased risk of adverse effects via direct damage to the skin, and can thus cause a paradoxical increase in pigmentation following treatment. This is particularly prevalent in patients with darker skin types, in whom this modality should be cautiously used or avoided. Despite the risks involved, there have been promising results in randomized trials using laser and light therapies (Table 4).

4.4.1 *Intense Pulsed Light*

Intense pulsed light (IPL) therapy has yielded some promising results in the treatment of melasma. A 16-week study by Wang et al. [40] comparing the application of 4 % hydroquinone cream plus IPL versus 4 % hydroquinone cream alone showed a 39.8 % improvement in the relative melanin index in the IPL group versus an 11.6 % improvement in the hydroquinone cream-only group. Furthermore, 35 % of participants in the IPL group achieved complete resolution of melasma versus only 14 % in the hydroquinone-only group. However, as with most therapies for melasma, relapse was observed, and improvement of melasma in this study decreased in 24.2 % of participants treated with IPL. The frequency of hydroquinone application was unclear and side effects were transient and mild.

In a 10-week, randomized, split-face study, Goldman et al. [41] evaluated the safety and efficacy of IPL in conjunction with triple combination cream versus IPL and a placebo cream. The triple combination cream contained hydroquinone 4 %, tretinoin 0.05 % and fluocinolone acetonide 0.01 %. At week 10, 57 % of patients in the triple combination cream group were clear or almost clear compared with 23 % in the inactive cream group. However, more irritation to the skin was observed in the triple combination group. Investigators and participants made all assessments subjectively.

In another recent study investigating the efficacy of IPL in melasma, Figueiredo and Trancoso [42] compared outcomes of IPL plus triple combination therapy versus triple combination therapy alone. MASI scores in the IPL group showed a 49.4 % reduction at 6 months from baseline and a 44.9 % reduction at 12 months from baseline. In the triple combination therapy-only group, MASI did not decrease from baseline to 6 months. It was unclear how long the IPL treatment sessions lasted or how often patients applied the triple combination cream. The investigators of the study also used their own 7-point scale for the assessment of melasma improvement. Crusting and hyperpigmentation were observed in the IPL-treated group, with resolution seen after 2 weeks.

4.4.2 *Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (QS-Nd:YAG) Laser*

Wattanakrai and colleagues [43] conducted a randomized, split-face trial comparing the use of Q-Switched Neodymium-Doped Yttrium Aluminum Garnet (QS-Nd:YAG) laser versus hydroquinone for the treatment of melasma. Participants exposed half of the face to 1,064 nm QS-Nd:YAG laser treatment for five sessions at 1-week intervals while 2 % hydroquinone was applied to the other half of the face. They found that the laser-treated side of the face achieved an average 92.5 % improvement in relative lightness index versus 19.7 % improvement on the hydroquinone-treated side. There was also a 75.9 % improvement in the modified MASI (mMASI) score on the laser-treated side versus a 24 % improvement on the hydroquinone-treated side. Subjects were more satisfied with the laser-treated side than the side treated with topical cream. Although the differences observed between groups were significant, all patients had recurrence of melasma. Adverse effects were notable in patients who received additional laser treatments following the study period, which included disfiguring mottled hypopigmentation, irritation, and rebound hyperpigmentation. In addition, all patients in this study had recurrence of melasma at the 12-week post-treatment follow-up visit.

In a 6-week, randomized, split-face study conducted by Park et al. [44], the efficacy of combination therapy 1,064 nm QS-Nd:YAG laser with 30 % glycolic acid peels was evaluated and compared with laser therapy alone, with exposure of laser to the entire face followed by exposure of one-half of the face to glycolic acid peels for three sessions at 2-week intervals. Results showed that the side treated with QS-Nd:YAG treatment plus glycolic acid peels showed an average improvement of 32.6 % in mexameter readings when compared with a 22 % improvement in the laser-only treated side. In addition, a 37.4 % improvement in the mMASI score in the combination treatment side was found when compared with 16.7 % on the laser-only treated side.

Kar and colleagues [45] carried out another study that explored the efficacy of QS-Nd:YAG laser versus glycolic acid peels. In this randomized study, three study groups were compared—low-fluence QS-Nd:YAG at weekly intervals versus glycolic acid peels at 2-week intervals for six sessions versus high-fluence QS-Nd:YAG at 2-week intervals. Results showed that the MASI score was significantly improved in the group receiving low-fluence QS-Nd:YAG when compared with the group exposed to high-fluence QS-Nd:YAG or glycolic acid peels. However, all groups showed an increase in MASI scores at the 12-week post-treatment follow-up visit. Adverse effects were commonly seen in the high-fluence QS-Nd:YAG group, with mottled confetti-like hypopigmentation observed in many patients.

4.4.3 Pulsed-Dye Laser

Pulse-dye laser (PDL) is a laser treatment that targets the vascular component of melasma and appears to be a new, promising therapeutic option for melasma. In a split-face study in 18 Caucasian women using triple combination therapy and PDL for 4 months, Passeron and colleagues [46] showed a statistically significant decrease in MASI score on the combination side, with a statistically significant continued decrease at the 2-month follow-visit. Post-inflammatory hyperpigmentation was notably observed in three patients, all of whom had dark skin (Fitzpatrick IV skin type). The continued decrease in melasma following treatment provides some optimism for a therapy that can help prevent relapse of melasma, which is a common occurrence.

4.4.4 Fractional Photothermolysis

In a randomized, split-face study, Hong et al. [47] sought to determine the efficacy of a single session of fractional photothermolysis on one-half of the face compared with 5 % trichloracetic acid chemical peel applied to the other half of the face for melasma. Both treatments were found to be equally effective, with the MASI score improved at 4 weeks in both groups and no significant difference between the groups. There was a high recurrence rate noted at 12 weeks, with post-inflammatory hyperpigmentation present in about one-third of patients.

4.4.5 Fractional Laser Therapy

In a randomized controlled, split-face study carried out by Wind et al. [48] comparing non-ablative 1,550 nm fractional laser therapy (FLT) versus triple combination therapy, they found that FLT produced increased pigmentation and a higher incidence of post-inflammatory hyperpigmentation than triple combination therapy. Patients were also found to prefer the triple combination therapy to the laser therapy at 6 months. In a similar study carried out by Kroon et al. [49] the use of non-ablative FLT was compared with daily application of triple combination cream. The recurrence rate was found to be the same for both groups after 6 months, and the Physician Global Assessment (PhGA), melanin index, and MASI scores showed no statistically significant differences between the two groups.

5 Discussion

5.1 General

The treatment outcomes in the trials reviewed were both subjective and objective. In many studies, treatment outcome was determined by scoring systems or scales based on a clinical exam, image review or a Wood's lamp examination, none of which are validated. The most common scoring system was the MASI, which uses four areas of the face in which the area of involvement, as well as darkness and homogeneity, are measured for score calculation. Recent validation of this score has determined that measurement of homogeneity is no longer needed. Another non-validated scale, the melasma severity scale, which measures changes in lesions using a scale from -2 to $+2$, was also used. Many investigators designed their own scales. In addition to the numerous scoring systems used, there was also much variation in the descriptors used to describe treatment outcome (e.g. 'good' vs. 'excellent'), which made it difficult to compare results across studies. Objective measurements of treatment outcomes were used in some studies to gauge improvement. This was accomplished using reflectance spectrophotometry, such as a mexameter or colorimeter, direct measurement of lesion size, or histological analysis before and after treatment. Some studies, particularly those evaluating laser and light therapy efficacy, used a mMASI score based on the confined portion of the malar surface used, versus the entire face as used in traditional MASI score calculation.

5.2 Recommendations

Topical hydroquinone appears to be the most extensively studied treatment for melasma and has been shown to be one of the safest and most effective therapies. In particular, topical triple combination therapy, containing hydroquinone, appears to be the most effective initial therapy for melasma. This combination uses tretinoin to enhance epidermal penetration of hydroquinone, while the topical steroid helps to decrease cellular metabolism and melanin production and provides protection against irritation from tretinoin [50]. Hydroquinone 4 % with sunscreen use is an alternative as well as dual combination therapy, or tretinoin or azelaic acid monotherapy. Protection from sun exposure is recommended with limited time outdoors and use of protective clothing and hats, as well as daily use of a high sun protection factor (SPF) ($\geq$30) sunscreen.

Other depigmenting agents, such as vitamin C, have been found to be less irritating than hydroquinone, and may be suitable for patients who cannot tolerate hydroquinone. Azelaic acid, another depigmenting agent, was found to be as effective as hydroquinone, but with a greater incidence of adverse effects, such as erythema and irritation. The depigmenting agent rucinol, or 4-*n*-butylresorcinol 0.5 %, was found to be well tolerated and effective in decreasing skin pigment when compared with placebo [15]. Thiospot® treatment also showed efficacy in forehead melasma, but it remains to be seen if this treatment has the same effect on

other parts of the face where melasma is prevalent, such as the cheeks and chin. Topical tranexamic acid showed no benefit in the treatment of melasma and had an increase in adverse effects associated with its use. Use of oral tranexamic acid may be effective in the future, as more evidence using this agent is acquired. Two percent kojic acid appears to be of benefit when added to 10 % glycolic acid and 2 % hydroquinone in the treatment of melasma.

Topical retinoids have shown varying degrees of effectiveness in the treatment of melasma. From the studies reviewed, tretinoin seems to be effective as monotherapy, but the time for improvement usually requires many months. There is also a high risk for skin irritation.

The chemical peeling agents reviewed did not show consistent efficacy in the treatment of melasma. Their use often resulted in low tolerability and increased risk of hyperpigmentation. Glycolic acid peels were not found to be more effective than topical preparations such as hydroquinone. Likewise, salicylic acid peels were not more effective than topical depigmenting agents and also tended to have a high rate of post-inflammatory hyperpigmentation. Due to the adverse effects associated with chemical peels, such as burning, bleeding, and increased risk of hyperpigmentation, they are considered second-line agents and should be limited to refractory melasma cases and used judiciously in darker-skinned individuals who are at higher risk of post-inflammatory hyperpigmentation.

Laser and light therapies have yielded mixed results. IPL therapy has been shown to be effective in improving melasma but is characterized by a high relapse rate. QS-Nd:YAG lasers appear to have detrimental effects on melasma, with increased risk of hyperpigmentation and a very high rate of relapse following treatment. PDLs, which target dermal vessels, are an exciting and promising new therapeutic approach for melasma, and have also been shown to delay relapse. Fractional light therapy appears to have a very high risk of post-inflammatory hyperpigmentation in patients who use it, as well as low tolerability. In general, laser and light therapies show the best response in lighter-skinned individuals. They are considered third-line agents for the treatment of melasma and should be used very carefully, particularly in dark-skinned patients. More research is needed to assess their safety.

5.3 Limitations

Despite the variety of treatments currently available for melasma, there exists no single therapy with guaranteed efficacy. The evidence in many studies is not strong and is compounded by poor and underpowered study designs. In addition, there is a lack of well-designed, placebo-controlled studies, making it difficult to compare treatments and assess statistical significance and validity.

Due to the clinical heterogeneity of the studies included, such as differences in Fitzpatrick skin type, melasma type, duration and severity of melasma, and age, statistical pooling of the data was not possible. Therapies also varied in their dosages, duration, treatment frequency, and fluences for laser therapy, making it difficult to compare studies. Future trials should be conducted for 6–12 months or longer to determine long-term effects. In addition, inclusion criteria such as skin type, duration of melasma, type of melasma, and age should be well defined and matched at baseline. Instruments for objective assessment of outcomes, such as reflectance spectrometry, and histologic analysis, are also recommended. There were several studies in which information regarding the method of randomization or blinding was not included, compromising validity and raising concern over bias. The MASI score has been validated and revised, creating the mMASI score [51]. Future studies should use this new scoring system.

Access to sunscreen was also not always clear in the studies reviewed. For example, several studies did not indicate whether participants were given sunscreen samples or if they were expected to purchase sunscreen independently. No randomized clinical trials have been designed to evaluate the extent to which sunscreen prevents or treats melasma. Sunscreen use alone should be evaluated in future randomized clinical trials to determine the minimal level needed to treat and prevent melasma. In addition, studies should be started after the summer to avoid seasonal effect of sun exposure. The sunscreen SPF and frequency of application used as part of interventions should be standardized in future studies.

Quality of life assessments were performed in very few studies. This is an important assessment to include, since melasma has been shown to have a detrimental impact on quality of life. The effect of treatment on patients should not only assess the degree of clinical improvement but the emotional and psychological effects as well. Quality of life measures and participant assessments of treatment outcome should be part of future study designs.

6 Conclusion

Despite the many treatments available for melasma, no definitive panacea exists for the treatment and prevention of this often-recalcitrant skin condition that affects millions of people worldwide. More research is needed to determine the optimal treatment regimen for melasma. The relapsing course of this condition makes it a difficult condition to manage clinically. The negative social and psychological impact of melasma on patient quality of life underscores the need for further research in developing effective therapies for melasma.

The existing evidence suggests that topical depigmenting agents, particularly those containing hydroquinone in conjunction with a steroid and retinoid, are most effective and safe for the treatment of melasma. Hence, first-line therapy for melasma should include hydroquinone alone or in conjunction with a topical steroid and retinoid (triple combination therapy). Tretinoin therapy, as well as a number of other agents, have shown to be somewhat efficacious in the management of melasma, while the safety and efficacy of chemical peels and laser and light therapies in the treatment of melasma has yet to be established. Chemical peels and laser and light therapies have produced mixed results, with an increased risk of irritation and subsequent hyperpigmentation, particularly in darker-skinned individuals. As evidenced by the studies reviewed, the long-term treatment for melasma remains unsatisfactory. A better understanding of the etiology of melasma will allow for the development of more targeted and effective therapies in the future.

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