REVIEW

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Systematic review of melasma treatments: advantages and disadvantages

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ABSTRACT

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INTRODUCTION

Melasma or chloasma is a common acquired dermatological condition that primarily affects the woman. This condition describes clinically as chronic and relapsing irregular macules or patches hyperpigmentation that occurs commonly on the face, predominantly attributed to UV exposure. UV radiation induces oxidative stress, which stimulates the melanocyte to synthesis melanin. While melasma does not present any health risk, it can cause significant psychological impact to many patients.[1,2]

The pathogenesis of melasma remains unknown, but multiple factors including UV exposure, genetic factor, inflammation and female sex hormones have been implicated and reviewed.[3] Melasma is classified according to clinical and histological features. Three common type melasma on face are centrofacial, malar, and mandibular. Extra-facial melasma can occur in the neck, sternum, and upper extremities. Based on pigment location, it may be epidermal, dermal or mixed.[3,4] This classification is important to define treatment options and prognosis.

Treatment of melasma generally starts with management risk factors, UV protection and clearing of the lesion with the fewest possible adverse effects. The principles of therapy include inhibition synthesis melanin pathway, a decrease of melanosome transfer from melanocytes to keratinocytes, and acceleration melanin remove pathway.[5] This research was to define available treatments for melasma and determine advantages and disadvantages, including topical, oral and procedural.

METHODS

The data search on Medline, Cochrane library and PubMed for articles published from January

2011 to June 2020 using keywords 'melasma' OR 'chloasma' AND 'treatment' AND 'meta analyzes' OR 'RCT' OR 'comparative' OR 'review'. The studies were categorized according to the type of treatment: topical, oral and procedural. Only RCTs, comparative, prospective, retrospective and systematic reviews focusing on melasma treatments in English were extracted, analyzed and discussed. Studies in the community, dermatology clinic and hospital were considered. The resulting measure reviewed includes outcomes, advantages and disadvantages of treatment.

RESULTS

The online literature search resulted in 197 citations (**F 1**), 42 met inclusion criteria and were included in this review. The total sample size was 2314 subjects, with each study including between 12 to 160 subjects. The time length of each study between 3 to 48 weeks. Thirty-four studies were randomized control trials, three were comparative, 2 were retrospective and 3were prospective. Below, we review each of these groups of treatment.

Topical treatments

Hydroquinone (HQ)

A topical agent is known as the first-line treatment of melasma. Topical agents in melasma treatment can be used as monotherapy, dual therapy, or triple therapy combination.[6,7] Hydroquinone (HQ) or known as dihydroxy benzene, is one of the topical agents that can inhibit DOPA conversion by tyrosinase enzyme inhibition, affects melanocytes structures and cause necrosis of melanocytes that can inhibit the melanogenesis process.[6-8] It is known that 2-4% HQ cream is

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therapy compared with combined cream based on MASI score, although the difference between MASI score was not significant. Hassal *et al.* study reported that 5% TA cream was more effective than 1% flutamide topical cream without adverse effects were reported.[15] The Janney et al. study also showed that TA cream was safer than HQ cream as monotherapy treatment, although it could cause erythema, skin irritation, xerosis, and scaling in long term usage.[16]

Kojid acid (KA)

Kojid acid (KA) or 5-hydroxy-2-hydroxymethyl-4-pyrone acts by inhibiting the production of free tyrosinase.[17,18] Combination KA and HQ were reported as superior depigmenting agent compared with other combinations. Kojic acid may cause erythema and contact dermatitis. Kojic acid has a better effect when combined with other topical agents. A single-blind RCT study by Deo *et al.* reported that kojic acid more effective in decreased MASI score compared with 2% hydroquinone.[17] It is different from Yenny's study showed 5% methimazole has a higher effect in decreasing MASI score and safer than 4% kojic acid.[18]

Cysteamine

Cysteamine is an L-cysteine product metabolism that acts as an anti-oxidant and antimutagenic agent. Cysteamine inhibits DNA polymerase, and cell progression that inhibits the melanogenesis process and can be used as alternative melasma treatment topical agents.[19,20] Farshi *et al.* study in 40 Indian patients reported that cysteamine cream was effective to treat melasma based on decreased MASI score compared to placebo.[19] It also reported a small number of adverse effects like 1st-grade erythema, itching and 1st-grade burning.[19] Similar study in 2015 by Mansouri *et al.* also showed that 5% of cysteamine cream was effective in treating melasma compared to placebo.[20]

Combination topical agents

Several studies reported the combination between 4% HQ cream and tretinoin cream (either 0.025% or 0.05%).[21-23] Gold *et al.* study in 2013 showed that a combination between 4% HQ cream and 0.05% tretinoin cream could reduce duration therapy compared to monotherapy and increased patients' quality of life significantly at the end of treatment.[21] Similar result was found in Grimes study that combination therapy can reduce the duration of therapy. This study also showed adverse effects

could treat mild melasma, but if it uses more than recommended duration, it can make melasma worsen than before treatment. It found that 33% of respondents felt their melasma was worsened (they suffered from telangiectasia, acneiform eruption, hypertrichosis) compared with before treatment.[28]

Table 1. Topical melasma treatment studies

Author, year, study design	Treatment	N	Advantages	Disadvantages
Adalatkhah and Sadeghi.[8] (2015) RCT, double-blind	1% flutamide topical cream versus 4% hydroquinone topical cream Duration: 4 months Evaluation: MASI, mexameter melanin assay	74 women	Flutamide has higher efficacy than hydroquinone while hydroquinone has a wide spectrum for melasma topical treatment.	Too much usage of flutamide topical drugs can cause mild systemic adverse effects
Monteiro *et al.*[9] (2013) RCT, single-blind	4% topical HQ vs. 0.75% KA (Kojid Acid) Duration: 12 weeks Evaluation: MASI	60 Indian patients	4% HQ has higher efficacy and faster onset of action than 0.75% KA. 4% HQ has melanosomes degradation, melanocytes destruction, inhibition of DNA and RNA synthesis.	Side effects (erythema and burning sensation) were noted in one patient (3.3%) receiving 0.75% KA and two patients (6.7%) receiving 4% HQ cream. KA was safer than HQ.
Yenny & Lestari.[10] (2013) RCT, single-blind	Arbutin 4% (hydroquinone derivatives) Duration: 2 months Evaluation: MASI	20 Padang patients	Arbutin is no toxic to melanocytes, safer than hydroquinone, acts as an inhibitor of melanosome tyrosinase activity.	All respondents feel reddish and warm on their face
Navarrete *et al.*[11] (2011) A comparative study, double-blind	4% niacinamide cream on one side of the face and 4% HQ cream on the other face side Duration: 8 weeks Evaluation: MASI, photography, colorimetric, histopathology by biopsy, chromameter, PGA	27 patients	4% niacinamide was effective in around 40% patient. Niacinamide can be used in long term usage âmast cell infiltrate,â pigmentation, inflammatory infiltrate, and # solar elastosis in melasma skin and safer than 4% HQ cream.	2 (7%) patients suffered from erythema, burning on the niacinamide side, and 18 patients (5%) suffered from that at HQ side and pruritus. Most of them were mild for niacinamide and moderated for HQ.
Farshi.[12] (2011) RCT, double-blind	4% hydroquinone cream (for 15 women) and azelaic acid cream (for 14 patients). Duration: 2 months applied twice daily. Evaluation: MASI	29 Iran women	20% azelaic acid cream more effective than hydroquinone 4% in reducing mild melasma. Azelaic acid acts as a tyrosinase inhibitor inhibits DNA synthesis of melanoma cell line without resulting dangerous side effect like ochronosis	Local irritation more occurs with azelaic acid. Severe adverse effects (pruritus, erythema, irritation) and allergic sensitization more common with hydroquinone cream.
Bansal *et al.*[13] (2012) RCT, open-label	20% AZA (Azelaic Acid) versus low-fluence 1064-nm Q-Switched Nd: YAG Laser versus combination both of them Duration:12 weeks Evaluation: MASI	60 patients	Better than low-fluence 1064-nm Q-Switched Nd: YAG Laser in melasma treatment	Local irritants (burning, irritants, itching)
Ebrahimi and Fatemi.[14] (2014) RCT, double-blind	Topical solution 3% TA (Tranexamic acid) on one side of the face, and topical solution of 3% hydroquinone + 0.01% dexamethasone on the other side two times a day. Duration: 12 weeks Evaluation: MASI every four weeks, photography at week 12	50 Iran melasma patients	Topical tranexamic acid (TA) safer than oral TA.	Erythema, skin irritation, xerosis, and

Janney *et al.*[16] (2019)\ RCT, single-blind	topical 5% TA solution for group A and 3% HQ cream for group B Duration: 12 weeks Evaluation: MASI, serial photograph	100 patients	TA cream is safer than HQ cream as mono-therapy	Mild erythema and irritation
Deo *et al.*[17] (2013) RCT, single-blind	Group A (kojic acid 1% cream), group B (kojic acid 1% + hydroquinone 2% cream), group C (kojic acid 1% and betamethasone valerate 0.1% cream), group D (kojic acid 1%, hydroquinone 2%, and betamethasone valerate 0.1% cream). Duration: 12 weeks Evaluation: MASI, Wood's light lamp	80 patients	Group B is more effective treat melasma. 60% excellent â MASI score in group B, followed by group A and D (25% excellent reduction) and group C (10%, excellent reduction). Kojic acid and hydroquinone are tyrosinase inhibition that can lighten skin due to antioxidant activity that # depigmenting effect and inhibits melanogenesis.	Solitary patients in group A and two patients in group B had burning sensation while in group D only one person who had acneiform eruptions.
Yenny.[18] (2018) RCT, single-blind	5% methimazole cream (right cheek) than 4% kojic acid (left cheek) Duration: 12 weeks Evaluation: MASI	90 Padang patients	Both methimazole and kojic acid cream have in the same way in inhibiting the activity of tyrosinase (kojic acid inactive chelates the Cu that have a role in tyrosinase process and methimazole inhibit peroxidase) that has the main role in melanogenesis.	5% methimazole has a higher effect in decreasing MASI score and safer than 4% kojic acid. Redness, itching, and burning
Farshi, Mansouri, Kasraee.[19] (2017) RCT, double-blind	cysteamine cream and placebo Duration: 4 months Evaluation: skin colorimetry, dermacatch, MASI scores, patient questionnaires, and Investigator Global Assessments (IGAs).	40 Indian patients with Fitzpatrick skin types III, IV, and V (20 people got cysteamine cream and 20 people got place during that treatment)	Cysteamine cream can be used as an alternative treatment. Concentration is a radioprotector that can â tyrosinase activity and # produce pheomelanin, inhibit DNA polymerase and cell progression that inhibit melanogenesis.	Erythema grade and itching grade I, dryness, burning grade I).
Mansouri *et al.*[20] (2015) RCT, double-blind	5% Cysteamine cream or placebo Duration: 4 months Evaluation: MASI, Investigator's Global Assessment (IGA)	53 people with Fitzpatrick skin type III, IV and V	Cysteamine can be used as a melasma topical treatment alternative. Cysteamine is inhibitors of peroxidase and tyrosinase, inhibit melanin synthesis that produces depigmentation	Erythema, burning, itching, or and dryness.
D				
Gold *et al.*[21] (2013) RCT, open-label	4% Hydroquinone + 0.05% Tretinoin Cream every evening Duration: 24 weeks Evaluation: MASI, Patient quality of life questionnaire	37 patients (only 34 completed it)	Shorter therapy duration compared (effects can be seen significantly since four weeks) to other topical/ Patient quality of life # from 78% felt embarrassed about their skin at week four into only 4% that felt embarrassed at week 24	A few respondents complained of erythema, peeling, burning, dryness, and stinging
Grimes dan Watson.[22] (2013) RCT, single-blind	Combination 4% hydroquinone skin + tretinoin cream 0.025% Duration: 12 weeks Evaluation: MASI	20 Female patients with Fitzpatrick skin types III to VI	Shorter duration therapy than tretinoin or hydroquinone monotherapy.	Fewer respondents complained of peeling, dryness, erythema, and stinging sensation

Ibrahim *et al.*[23] (2015) RCT, single-blind	Group I (4% hydroquinone), group II (4% hydroquinone + 10% glycolic acid cream), group III (4% hydroquinone + 0.01% hyaluronic acid cream), group IV (4% hydroquinone + 10% glycolic acid + 0.01% hyaluronic acid), and group V (placebo cream). Duration: 6 months Evaluation: mMASI, dermascope	106 Egypt patients (100 completed)	Group III (4% hydroquinone + 0.01% hyaluronic acid cream) was more effective efficacy than group I and had less irritant than others. Group II (4% hydroquinone + 10% glycolic acid cream) was effective for dermal melasma.	Group II showed the highest rate severe of side effects (irritant, mild pruritus, erythema) followed by group IV (70%) of patients (10% of the patient complained of mild pruritus, 30% of patients have mild-to-moderate erythema, 20% have mild scaling, and 10% patients suffered from moderate crustation), the group I (60% of patients), group III (20%) patients were suffering from mild pruritus). No side effect was reported in group V. Recurrence was reported in 6 patients (30%) in group I and four patients (20%) in group III
Ahmad *et al.*[24] (2019) RCT, single-blind	Combination cream between: 4% Hydroquinone (HQ), 0.05% tretinoin 0.05%, and 0.01% fluocinoloneacetonide Duration: 8 weeks Evaluation: MASI	22 Iran women	Each composition maximizes the work of other compositions and minimizes side effects. # Skin density because of remodeling effect on collagen and elastin fibers and deposition of glycosaminoglycans. Fluorinated â irritation potential. No significant changes were found in skin hydration, erythema, sebum, and pH. Twice weekly application of combination cream for six months was more effective and had a lower relapse in severe melasma.	Almost all participants experienced scaling, some degrees of pruritus, and erythema around the first month of cream usage
Pekmezci *et al.*[25] (2019) Retrospective, single-blinded	Combination cream between Azelaic acid (4%), methylprednisolone aceponate (0.04%), hydroquinone (1.6%), and salicylic acid (2%). Duration: 6 months. Evaluation: MASI & PSAS	68 Turkey female patients with Fitzpatrick skin types II-IV.	62% of the total decrease in MI (Melanin Index) in the first three months. The active material combination can abort undesirable effects of another one and creates synergic effects	Irritations were expressed at the beginning of treatment for the first two weeks. Hypertrichosis occur at 6th month of therapy
Fragoso, Tirano, Ponce.[26] (2015) RCT, single-blinded	Triple combination that consist of arbutin 5% + kojic acid 2% + glycolic acid 10% for group A (33 patients) & hydroquinone 4% from group B group (30 patients). Both groups applied creams daily at night. Duration: 3 months Evaluation: MASI & the Spanish-Melasma Quality of life questionnaire [Sp-MelasQoL])	63 Mexicans women	The triple combination is as effective as hydroquinone usage due to the material combination.	Erythema, burning and irritation in both groups, although most occur in group A.
Sardesai, Kolte, dan Srinivas.[27] (2013) RCT	Regimen I (3% Kojic acid +2% Vitamin C cream), regimen II (20% Azelaic acid cream), regimen III (2% Hydroquinone + 0.025% Tretinoin + 0.1% Mometasone furoate cream), regimen IV (5% Arbutin + 0.5% Glabridin cream), regimen V (5% Arbutin + 10% Glycolic acid + 3% Kojic acid cream) Duration: 3 months Evaluation: MASI & Wood light lamp	160 Indian patients that consist of 127 females and 33 were males with age above 18 years	The combination between regimen such as Tyrosinase inhibitors (azelaic acid, hydroquinone, kojic acid, arbutin, glabridin), Inhibitors of melanin production (ascorbic acid, etc.) and non-selective suppressor of melanogenesis (corticosteroids)	Erythema, dryness, burning sensation,

Oral treatments

Tranexamic acid (TA)

An oral agent is another additional treatment for melasma. Several studies about oral treatments of melasma have been studied for a long time and remain an interesting topic to study. Tranexamic acid (TA) is currently used via oral, topical, intradermal, and micro-needling. Multiple studies have documented the efficacy of TA in patients with melasma. A double-blind RCT study by Del Rosario et al. assessed the efficacy of TA 250 mg twice daily versus placebo in a 3-month study, followed by three months of sunscreen only. Thirty-nine patients completed the trial with outcomes mMASI decreased over time in both groups, with those on the TA group decreasing more than placebo groups at 12 weeks. No serious adverse events were reported, but side effects more occur in the TA group.[29] Another double-blind RCT study by Shin et al. assessed combination oral TA 750 mg daily with laser versus laser only showed greater improvement of MASI scores in the combination treatment group. Forty-four patients were completed for eight weeks of study. Oral TA medication might enhance the efficacy of laser treatment but require long durations of treatment to achieve noticeable skin lightening and were associated with several undesirable side effects.[30]

Polypodium leucotomos (PL)

There has been much interest recently in the use of polypodium leucotomos (PL) as an adjunct photoprotective agent in melasma. Mechanisms of PL include the promotion of the p53 suppressor gene expression, modulation of inflammatory cytokines, upregulation of endogenous antioxidant systems, and blockade of UV radiation-induced cyclooxygenase–2 expression.[31,32] Several recent studies have documented a beneficial effect in patients with melasma. A double-blind RCT study of 40 patients by Goh *et al.* assessed the efficacy of PL 240 mg twice daily versus placebo for 12 weeks. PL group has a significantly greater reduction in MASI score at 56 and 84 days of treatment.[33] In a randomized, placebo-controlled study of 40 patients by Martin *et al.* assessed the efficacy of PL 240 mg twice daily versus placebo. The PL group had significantly improved mean MASI. A photographic assessment revealed mild improvement in 43% of subjects receiving PL compared to 17% of placebo and marked improvement in 14% of subjects receiving PL compared to 0% of placebo. MelasQoL parameters were reported as worsened in 50% of placebo compared to 20% of PL subjects. Overall, this study stated the well-tolerated and effective PL as an adjunctive treatment option, but it is not efficient to consume orally twice daily for long weeks to treat melasma.[34]

Miscellaneous agents

There were several miscellaneous dietary supplements such as glutathione (GSH) and carotenoid. GSH is one of the most powerful endogenous antioxidants produced by cells in the human body and is a tripeptide of glutamate, cysteine, and glycine. Mechanisms that induce lightening of the skin include inhibition of tyrosinase and the ability to skew production of eumelanin to pheomelanin.[35,36] Previous double-blind RCT study with sixty patients was reported by Weschawalit et al., which evaluate glutathione as antiaging and anti-melanogenic. Patients were divided into three groups include GSH 250 mg daily, oxidized form (GSSG) 250 mg daily and placebo for 12 weeks. Its results tend to decrease UV spots and increased skin elasticity on GSH and GSSG groups compared with placebo. No major adverse events were reported, but increased serum transaminase occur on two patients, highlighting that blood chemistry should be performed.[37]

Nowadays, many natural agents were developed. Carotenoid is a naturally pigmenting extract from plants, algae, and photosynthetic bacteria that have effects on anti-inflammatory, antioxidant, and photoprotection aging.[38] A double-blind RCT study was performed by Teo et al. of 44 patients assessed efficacy 800 mg carotenoid versus placebo in 84 days. In the end, the median mMASI score significantly in both groups, and there was more decrease in the treatment group. Erythema score also showed greater improvement in treatment groups compare to placebo.[39]

Procedural treatments

Chemical peels

Several procedural treatments had been studied and interest to develop, such as chemical peel, micro-needling, and laser and light therapy. Chemical peels have been used in several studies, but most have not shown superior efficacy to topical agents.[40] Some evidence showed a moderate quality of serial chemical peels with glycolic acid (GA), salicylic acid, or trichloroacetate acid (TCA) were effective in melasma treatment. Superficial and medium depth peels have been used and generate a good result in melasma treatment, but chemical peels can cause irritation and inflammation that can lead to relapse of melasma.[41,42]

Several studies reported glycolic acid as a chemical peeling agent of the skin. A double-blind, RCT study in 40 Indian patients with melasma by Mahajan *et al.*[43] found that low potency triple

Table 2. Oral melasma treatment studies

Author, year, study design	Treatment	N	Advantages	Disadvantages
Del Rosario et al. (2017) RCT, double-blind	Group A TA 250 mg BID + sunscreen Group B Placebo BID + sunscreen Duration: 3 months baseline pills, six months evaluation with sunscreen only Evaluation: photography, mMASI, pill count, melanin index, QOL questionnaire	44 patients (39 completed)	Might treat moderate-severe melasma who do not respond with standard therapy No serious adverse effect	Side effect occurred in 63.6% of patients on Group A, gastrointestinal discomfort, change in menstrual period, myalgias, headache, arthralgias, blurry vision
Sin et al. (2013) RCT, double-blind	Combination oral TA 750 mg daily + low-fluence QSNY laser versus low-fluence QSNY laser treatment only Duration: 8 weeks Evaluation: Photography, mMASI,	48 patients (44 completed)	Oral TA medication might enhance the efficacy of laser treatments Reduce refractory melasma by conventional treatment	Require long durations of treatment to achieve noticeable skin lightening and are associated with several undesirable side effects, including skin irritation and paradoxical post-inflammatory hyperpigmentation, especially in Asian patients
Goh et al. (2018) RCT, double-blind	PL 240 mg BID + topical 4% hydroquinone and sunscreen SPF 50 versus Placebo BID + topical 4% hydroquinone and sunscreen SPF 50 Duration: 12 weeks Evaluation: mMASI, skin colorimeter, photography, MelasQoL	40 patients (35 completed)	PL accelerates the pigmentation clearance of melasma compared to those treated with topical 4% hydroquinone and sunscreen alone. No significant side effects were reported throughout the study	PL usage alone is not recommended. It must be accompanied by sunscreen and avoidance of sun exposure during the peak hours of the day
Martin et al. (2012)	PL 240 mg BID + sunscreen SPF 45 versus Placebo + sunscreen SPF 45 Duration: 12 weeks Evaluation: MASI, Photography, MelasQoL	21 patients	PL is well tolerated and effective in patients with Melasma and importance as an adjunctive treatment option	Most patients were not interested in purchasing and ingesting an oral medication three times daily Less efficient to consume oral drugs three times a day for long weeks to treat melasma
Weschawalit et al. (2018) RCT, double-blind	Group A: GSH 250 mg daily Group B: GSSG 250 mg daily Group C: Placebo Duration: 12 weeks Evaluation: Melanin index (Maxameter), photography, TEWL, Corneometer, Cutometer, Visioscan	60 patients (57 completed)	Glutathione in both forms is well tolerated. No major adverse events took place during the study period.	Adverse reactions included pruritus, macular erythema, transient minute red spots on the skin, and tiredness Increases in transaminases occurred in two subjects highlighting the fact that blood chemistry should be performed even when individuals are taking over-the-counter supplements
Teo et al. (2015) RCT, double-blind	An oral supplement containing carotenoid + lightening cream versus placebo + lightening cream Duration: 84 days Evaluation: mMASI, photography, melanin and erythema index using Maxameter	44 patients (36 completed)	Active supplement carotenoid potentially has an adjunctive treatment No major side effects have reported	Need further larger scale and longer studies

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combination (HQ 2%, tretinoin 0.05%, fluocinolone 0.01%) and glycolic acid peels/ azelaic acid 20% cream resulted in a low significant reduction in MASI and VAS. Both low potency TC cream and GA/AA 20% cream combination are effective in treating melasma among Indian patients. All patients used broad-spectrum sunscreen with SPF 30 to minimize the side effects. Another study by Sarkar et al.[44] compared glycolic acid 35% peel, salicylic-mandelic acid, and phytic combination peels in 90 Indian patients with melasma for 20 weeks. The decrease MASI score in glycolic acid 35% peel, and salicylic-mandelic acid was significantly lower than phytic combination peels, but no significant difference between the glycolic acid peel and salicylic-mandelic acid peel. Salicylic-mandelic acid peel is a combination of alpha and beta hydroxy acid. Mandelic acid is an ideal peeling agent for sensitive skin because it is associated with a less stinging and burning sensation. Glycolic acid has a good response in Asian and Black patients with melasma.[44] Garg et al. compared the use of three different chemical peels: 35% GA full-face peel, 35% GA full-face peel followed by a 10% TCA spot peel, and 35% GA full-face peel followed by a 20% TCA spot peel once every 15 days in 30 patients. All the groups had a significant decrease in MASI. Hence, a combination of GA and TCA peels does not increase the efficacy of melasma treatment while they may increase the side effects.[45]

Salicylic acid peels are well tolerated in all skin types.[44] A randomized control trial by Balevi *et al.* compared 30% salicylic acid peel and 30% salicylic acid peel + vitamin C intradermally in 50 patients. MelasQoL and MASI scores decreased significantly in both groups. Salicylic acid peels combined with vitamin C intradermally produced better results in terms of the MASI and MelasQoL scores. The effect of salicylic acid peels increased when combined with intradermal vitamin C since it had no damage to the epidermis.[46]

TCA is a versatile chemical peeling that has the ability to create superficial, medium, and deep peels based on strength. A recent randomized study by Murtaza *et al.* compared a combination of 20% TCA peel + magnesium ascorbyl phosphate (MAP) cream once daily with TCA peels alone in 148 patients for six weeks. The combination group has shown a significant decrease in MASI scores than the chemical peel group only. The efficacy of TCA peel + MAP cream is more effective compared to TCA peel alone.[47] Another non-randomized control study by Puri compared 15% TCA peel and 35% glycolic acid peel in 30 patients. Both of the groups are significantly reduced MASI scores and equally effective in treating melasma.[48] TCA is stable, inexpensive, and causes no systemic toxicity. TCA has more side effects compared to glycolic acid peel, such as erythema, burning sensation, desquamation, hyperpigmentation, and cracking.[47,48]

Laser and light-based therapy

Laser and light-based therapy are additional therapy for melasma. They had an unpredictable response and also caused recurrent pigmentation symptoms. Intense Pulsed Light (IPL) therapy uses a flash lamp that emits noncoherent light with wavelengths between 515-1200 nm. The filter targets selective chromophores (melanin, hemoglobin) and is used to treat pigmentation disorders, including melasma. IPL therapy results in modest improvement on melasma patients with refractory to topical therapy alone.[5] Laser therapy also became an alternative to treat melasma, especially in refractory and resistance cases. Due to the high recurrence rate, laser therapy is only recommended for persistent melasma cases that have failed the other laser and light-based therapy modalities.[5,49]

A randomized trial by Goldman *et al.* compared IPL with a triple combination cream (TCC) and IPL with a placebo cream (PC) in moderate to severe melasma for ten weeks in 56 patients. Improvement in melasma was significantly greater in TCC and IPL than with placebo cream and IPL. This showed that IPL could be helpful to treat melasma if combined with an aggressive topical maintenance treatment to minimize pathways for the recurrence pigmentation.[50] Another similar study by Figueiredo & Trancoso compared IPL with TC cream versus TC cream alone in 62 patients for 48 weeks. Single-session IPL followed by TCC was more effective than TCC therapy alone.[51] In a randomized control trial, Shakeeb *et al.* also compared TCC alone, IPL alone, and IPL with TCC in 96 patients for eight weeks. MASI score reduction was 68.8% in group A, 62.5% in group B and 93.8% in group C. Decrease in MASI was higher in Group C compared to Groups A and B. Combination of IPL therapy and TCC is significantly more efficacious than IPL therapy and TCC alone.[52]

Low fluence Q-switched (LFQS) Nd: YAG laser was the most commonly evaluated laser in melasma. Several studies identified the combination of laser and laser alone shown some improvement in treating melasma.[5] Hence, laser monotherapy is not recommended in melasma due to recurrent pigmentation. The maintenance schedules must be continued altogether with topical treatment for melasma.[53] A prospective study by Hofbauer Parra *et al.* treated 20 patients with a low-fluence 1064-nm QS Nd: YAG laser for ten weeks. It was found

Table 3. Procedural Melasma Treatment Studies

Author, year, study design	Treatment	N	Advantages	Disadvantages
C				
Mahajan, et al. (2015) RCT, double blind	TC (HQ 2%, tretinoin 0.05%, fluocinolone 0.01%) versus GA peels/ AA 20% cream Duration: 12 weeks Evaluation: digital photography, MASI, VAS	40 Indian patients (38 completed)	GA peels improved surface texture, appearance, and photodamaged. The exfoliative effect of GA peels stimulates new epidermal growth and collagen.	Four patients from TC and three patients from GA/AA 20% cream experienced irritation, dryness, and photosensitivity
Sarkar *et al.* (2016) RCT, single-blind	Group A GA-35% peel Group B 20% Salicylic and 10% Mandelic acid Group C phytic combination peels Duration: 20 weeks Evaluation: MASI, photography	90 Indian patients	GA and SM acid peels are both equally efficacious and safe for treating melasma in Indian skin. SM peels are a more suitable tolerance for Indian skin. GA gives a good response in epidermal and melasma in Asian and Black patients.	Group A: 19% mild erythema and desquamation, 15% PIH Group B: 25% burning sensation Group C: 32% burning sensation
Garg *et al.* (2019) RCT, double-blind	Group A: 35% GA full-face peel Group B: 35% GA full-face peel + 10% TCA spot peel Group C: 35% GA full-face peel + 20% TCA spot peel Duration: once every 15 days for eight weeks Evaluation: MASI	30 patients	GA peels or in combination with TCA are resulting in a significant improvement in melasma.	Persistent local erythema, pruritus burning sensation, and transient hyperpigmentation. A combination of GA and TCA peels does not improve the efficacy, while they may increase the side effects.
Balevi *et al.* (2017) RCT, single blind	Group A: 30% SA peel Group B: 30% SA peel + vitamin C intradermally Both protected with SPF 15 or higher 2-3 times daily. Duration: every two weeks for two months Evaluation: MASI, MelasQoL	50 patients	SA peel + vitamin C mesotherapy is safe and effective for the treatment of melasma with no significant side effects and minimal downtime.	Mild to a moderate burning sensation.
Murtaza *et al.* (2016) RCT	Group A: 20% TCA peel + MAP 5% topical Group B: 20% TCA peel Duration: 6 weeks Evaluation: MASI	148 patients	The Efficacy of combination TCA and MAP is more effective compared to TCA peel alone.	Erythema, burning sensation, desquamation
Puri. (2012) Non-randomized Comparative	Group A: 15% TCA peel Group B: 35% GA peel Duration: every three weeks (maximum six times) Evaluation: MASI	30 patients	TCA has a versatile ability to create superficial, medium, and deep peels. It is stable, inexpensive, and causes no systemic toxicity.	Burning/ stinging, scarring, folliculitis, pain, hyperpigmentation, Post-peel cracking TCA had more side effects.
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Goldman *et al.* (2011) Randomized, single-blind	One side: IPL + TCC Contralateral side: IPL + placebo cream Duration: 2 sessions, at week 4 and 6 for ten weeks Evaluation: IGA	56 patients	A combination of TCC and IPL is an effective and safe treatment option for patients with melasma.	The combination of TC cream and IPL had more adverse effects than placebo cream and IPL. The adverse effects such as erythema, scaling, dryness, telangiectasia, and burning sensation.

Figueiredo & Trancoso. (2012) Randomized, open-label	Group A: IPL + TCC Group B: TCC alone Duration: 48 weeks Evaluation: MASI, IGA	62 patients	Single-session IPL combined with TCC treatment is safe and effective refractory mixed and dermal melasma.	Temporary side effects were associated with IPL treatment, such as mild erythema and pain.
Shakeeb *et al.* (2018) RCT	Group A: TCC alone Group B: IPL alone Group C: IPL + TCC Duration: 8 weeks TCC daily at night IPL 4 session every two weeks Evaluation: MASI	96 patients	The combination of IPL therapy and TCC is significantly more effective than IPL therapy and TCC alone.	Side effects are not mentioned.
Hofbauer Parra *et al.* (2016) Prospective	low-fluence 1064-nm QS Nd: YAG laser Duration: 10 weeks (interval one weeks) Evaluation: MASI	20 patients	low-fluence QS Nd: YAG laser is safe and effective for treating melasma. Long term effect was poor due to the high recurrence rate in monotherapy.	Temporary mild erythema and local warmth
Lee *et al.* (2013) RCT, double-blind	Group A: 1064-nm QSNYL + placebo chemical peeling Group B: 1064-nm QSNYL + Jessner's solution chemical peeling Duration: 20 weeks (2 weeks interval) Evaluation: MASI, PGA, the self-assessment	52 patients	Combination of Jessner's peel with low-fluence 1064-nm Q-switched Nd: YAG laser is a safe and effective method in the early course of melasma treatment.	Burning sensation during and after Jessner's solution Application.
Vachiramon*et al.* (2015) RCT, single blind	Low-fluence QSNd: YAG 1064 nm to the entire face vs. additional 30% GA peel to one side Duration: 16 weeks (5 weekly sessions) Evaluation: MASI, RL*I, patient self-assessment SPF 50 once daily	12 patients	No significant difference in relative lightness the index between both sides.	Burning or stinging, guttate hypopigmentation
Vachiramon *et al.*(2015) RCT, single blind	Low-fluence QSNd: YAG 1064 nm to the entire face (5 weekly sessions) vs. additional IPL on one side (3 sessions) Duration: 12 weeks Evaluation: MASI, RL*I, patient satisfaction	20 patients 18 completed	Both sides of the face showed significant improvement of R*LI and MASI. A more rapid improvement was observed on the combined side. Recurrence occurred on both sides.	Slight erythema and mild stinging on both sides and was resolved within one day.
Saleh *et al.* (2019) The prospective, randomized study, double-blind	Group I: micro-needling (6 sessions) + topical TXA Group II: micro-needling alone (6 sessions) Duration: 12 weeks (2-week interval) Evaluation: MASI	42 patients	Microneedling is safe and effective to decrease epidermal hyperpigmentation and dermal melanophages	Slight transient erythema and burning sensation
Budamakuntla *et al.* (2013) A prospective, randomized, open-label study	Group A: localized microinjection of TXA Group B: TXA + micro-needling Duration: 11 weeks (4-weeks interval) Evaluation: MASI, PGA, PtGA	60 patients	Micro-needling results in a good response of MASI scores due to the deeper and uniform delivery of medication.	Itching, burning sensation, and erythema in both groups.

that low-fluence QS Nd: YAG laser is effective in reducing MASI scores, but the recurrence rate was high.[54] Another study by Lee *et al*. compared 1064-nm QSNYL + placebo chemical peeling with 1064-nm QSNYL + Jessner's solution chemical peeling for 20 weeks in 52 patients. Significant decrease in MASI scores at eight weeks in all groups. There was no significant difference in MASI score, PGA, and self-assessment at 20 weeks.[55] Vachiramon *et al*. also compared low-fluence QSNd: YAG 1064 nm to the entire face versus an additional 30% GA peel to one side for 16 weeks in 12 patients. There was no significant difference between both treatments in RL*I and mMASI score. But patient self-assessment was more favorable in the combined treatment.[56] In another study, Vachiramon also compared low-fluence QSNd: YAG 1064 nm to the entire face versus additional IPL on one side for 12 weeks in 20 patients (18 completed), shown significant improvement in both sides of the face. Recurrence occurred on both sides.[57]

Microneedling

Microneedling uses a fine needle instrument, which is rolled over the skin to create some punctures. The treatment results in a wound-healing response and produces collagen and elastin. This technique is also used to enhance transdermal drug delivery through the stratum corneum. Microneedling decreases the risk of many adverse effects that can occur with conventional resurfacing modalities. Microneedling keeps the epidermis partially intact, and it hastens the recovery also minimalize the risk of infection and scarring.[58]

A prospective randomized study by Saleh *et al*. compared the efficacy of topical tranexamic acid with micro-needling versus micro-needling alone in melasma treatment. It has shown a significant decrease in MASI scores in both groups. There was a significantly higher reduction of MASI scores in topical tranexamic acid with micro-needling compared to micro-needling alone. Epidermal hyperpigmentation and dermal melanophages were significantly reduced after treatment. Microneedling alone produced a significant lightening effect, but topical TXA combined with micro-needling achieved more satisfactory results.[59] Another study by Budamakuntla *et al*. compared the therapeutic efficacy and safety of tranexamic acid microinjections versus tranexamic acid with micro-needling in melasma patients. The results showed a 35.72% improvement of MASI scores in the microinjection group compared to 44.41% in the micro-needling group. Tranexamic acid microinjection can be used as a potential and effective in melasma treatment. Microneedling group resulted in a better response to treat melasma because it attributed to the deeper and uniform delivery of medication through the microchannels.[60]

DISCUSSION

Melasma remains therapeutically challenging, despite various treatment options available with multimodality. Treatment efficacy can vary due to several factors, including variability in clinical presentation and response to treatment amongst different genders, skin phototypes, and ethnicities. The effect of treatment also depends on the treatment time, the usa0 141.r c4.9(e)-5(c)19(t)-

to the cellular level. However, the disadvantages of oral therapy are it may be unsuitable for those who do not want or cannot take oral medications for long days. The efficacy of oral agents can also influence by stomach acid and enzyme degradation.

From procedural treatment studies reviewed, skin micro-needling was reported resulting in sustained long-term improvement because it stimulates fibroblast proliferation, the release of growth factors and collagen production.[58] Microneedling keeps the epidermis partially intact and minimizes the risk of infection and scarring. However, not many studies have discussed the efficacy of micro-needling. Several studies have recommended a combination of topical agents to reduce side effects.[59,61] Laser and light-based therapy have a limited role in melasma treatment. Laser and light-based therapy had an unpredictable response and also caused recurrent pigmentation symptoms. Laser therapy became an alternative to the treatment of melasma, especially for patients with refractory and resistance cases.[5]

Regarding the methodology of the study, most of the studies in this review used outcome measures based on clinical examination and photographic evaluation. Serial photography is essential in the clinical management of hyperpigmentation, especially helpful when patients think treatment is not working. MASI score and mMASI score were the most common scoring for evaluation. In the case of melasma, a gradual reduction in the intensity of pigmentation over all the areas of the face simultaneously shows a positive response to treatment, even a small reduction in pigment intensity. However, because of the overdependence on the "area" variable, MASI or mMASI score is not adequate to reflect this positive response to treatment sensitively. Some studies also using non-validated measure outcomes such as patient self-assessment. The patient self-assessment has become as valuable as a professional's assessment to judge the progression of treatment over time. Physicians who treat patients with melasma should be aware of its profound psychosocial effects and the improvement that successful melasma treatment can have on self-esteem.

It is difficult to compare all the studies because many articles include a non-general term to evaluate the severity. No treatment for melasma has demonstrated truly satisfactory results, and so far, it is unclearly stated that these treatments have been demonstrated to prevent frequent relapses. With so many options, it can be hard to decide which treatment is the most optimal because the approach treatment of melasma depends on the region, type, and severity of melasma. Better studies using objective and validate outcome measures, a large sample size, and longer follow-up are needed.

CONCLUSION

In conclusion, the current state of the evidence suggests that some treatments with multiple modalities have their respective advantages and disadvantages. The choice of treatment modality must be adjusted according to the type of melasma, such as its severity, extent and location. A better understanding of melasma through further research may improve the therapy options with the least adverse effects.

CONFLICT OF INTEREST

None declared.

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All authors contributed to this publication.

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