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Review

Melasma – Updated Treatments

Mirna Šitum[1], Maja Kolić[1], Željana Bolanča[1], Ivana Ljubičić[1] and Bernarda Mišanović[2]

[1] Department of Dermatology and Venereology, »Sestre milosrdnice« University Hospital Center, Zagreb, Croatia
[2] Department of Dermatology and Venereology, »Virovitica«, General Hospital, Virovitica, Croatia

A B S T R A C T

Melasma is a common, acquired facial skin disorder, mostly involving sun-exposed areas like cheeks, forehead and upper lip. Melasma occurs in both sexes, although almost 90 percent of the affected are women. It is more common in darker skin types (Fitzpatrick skin types IV to VI) especially Hispanics/Latinos, Asians and African-Americans. The onset of the melasma is at puberty or later, with exception of darker skin types, who tend to develop this problem in the first decade of life. The etiology is still unknown, although there are a number of triggering factors related to the onset of melasma. The most important are sun-exposure and genetic factors in both sexes, while hormonal activity has more important role in females. In addition, stress and some cosmetic products and drugs containing phototoxic agents can cause outbreaks of this condition. Melasma should be treated using monotherapies or combination of therapy, mainly fixed triple or dual combinations containing hydroquinone, tretinoin, corticosteroids or azelaic acid. Modified Kligman's formula is also very effective. Above mentioned therapy regimens in combination with UVA and UVB blocking sunscreens are mostly effective in epidermal melasma. Discontinuation of the use of birth control pills, scented cosmetic products, and phototoxic drugs coupled with UV protection are also benefitial in clearing of melasma. Alternative treatment including chemical peels and glicolic acid, seem to have the best result as a second line treatment after bleaching creams. Laser treatments show limited efficacy and should rarely be used in the treatment of melasma. Combining topical agents like hydroquinone, tretinoin and a corticosteroid in addition to sun avoidance, regular use of sunscreen throughout the year and patient education is the best treatment in this difficult to treat condition.

***Key words**: melasma, hyperpigmentation, hydroquinone, tretinoin, corticosteroids, fotoprotection*

Introduction

Melasma is common acquired facial skin discoloration, mostly involving cheeks, forehead and upper lip. Generally, melasma can occur in both sexes, but almost 90 percent of the affected are women. Though any race and skin type can be affected, darker skin types (Fitzpatrick skin types IV to VI) especially Hispanics/Latinos, Asians and African-Americans, have higher incidences of melasma. The onset of the melasma is mostly noted at puberty or later, with the exception of darkly races from India, Pakistan and the Middle East who tend to develop this problem in the first decade of life[1].

The major determinant of normal skin color is the activity of melanocytes, quantity and quality of pigment production and not the density of melanocytes[2]. Melanocytes contain a unique intracytoplasmic organelle, the melanosome, which is the site of melanin biosynthesis. Compared with lightly pigmented skin, dark skin has melanosomes that contain more melanin and are larger in diameter. Melanosomes contain tyrosinase, a copper-containing enzyme, which catalyzes the conversion of L-tyrosine to L-dopa and L-dopa to L-dopa-quinone in melanin synthesis[3].

The definite etiology of melasma is uncertain but there are number of the triggering factors that are related with the onset of the condition. Exposure to sunlight and genetic factors[4] are significant causative agents in both sexes, with the addition of hormonal influence in female. In addition, stress[5] and some cosmetic products and drugs containing phototoxic agents can cause outbreaks of this condition. Uncontrolled sunlight exposure is considered the leading cause of melasma, especially in individuals with a genetic predisposition to this condition. Some studies have shown that melasma typically outbursts in the summer months and fading during periods of sun avoidance[6]. Melasma is often associated with

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the female hormones estrogen and progesterone. It is especially common in pregnant women[7] (chloasma), women who are taking birth control pills[8] (oral contraceptives) and women taking hormone replacement therapy[9] (HRT) during menopause. Chloasma (»mask of pregnancy«) commonly decreases or disappears after parturition, especially in lightly pigmented women.

Melasma presents as brown, gray or blue macules that coalesce into patches with irregular outline emerging mostly on sun exposed skin. The three major patterns based on clinical findings are the centrofacial pattern (the most common pattern that occurs in two thirds of melasma patients and affects forehead, nose, chin and medial cheeks), the malar pattern (appears in about 20%, only cheeks and nose involved) and the mandibular pattern (appears in 15% of patients, strikes the skin overlying the mandibula)[2].

Based on Wood's lamp examination there are three major histological types: epidermal (good response to topical therapy), dermal and mixed. According to some authors there is a fourth type – Wood's lamp inaparent – seen in patients with darker skin type[10].

Treatment

Besides skin changes which can mutilate persons appearance, melasma can cause emotional disturbance. Treatment of melasma is demanding and, sometimes, frustrating process due to frequent relapses and varying success. Reduction of the symptom expression, affected area, relapses and cosmetic disfigurement in combination with minimal adverse events are considered to be the goals of treatment[11]. Discontinuation of the use of birth control pills, scented cosmetic products, and phototoxic drugs coupled with UV protection[12] are obligatory measurements in combination with topical treatement[2]. Topical treatments include hydroquinone cream which is the most prescribed agent for melasma in monotherapy or can be used in combination with tretinoin, azelaic acid or steroids and is considered the gold standard especially for epidermal melasma. Hydroquinone, tretinoin and azelaic acid are tyrosinase inhibitors and act directly on melanogenesis, in contrast to physical therapy like chemical peels, and lasers that remove melanin, rather than inhibiting melanocytes. If melasma outbursts during pregnancy, treatment is postponed since it usually withdraws after parturition, but the use of broad spectrum sunscreens is essential[13].

Topical treatment

Hydroquinone

Hydroquinone (1,4-dihydroxybenzene) competes with tyrosine, preventing the enzymatic oxydation of tyrosine to dopa – melanin precursor[2]. HQ also inhibits the formation and increases degradation of melanosomes[14] and inhibits the DNA and RNA synthesis of melanocytes[15]. HQ is one of the most commonly used depigmentating agents. It is available at concentrations ranging from 1.5 to 5%. Effectiveness of the HQ is related directly to the concentration of the preparation, to the vehicle used and to the chemical stability of the final product[16]. Higher concentrations (over 2%) are disposable only by prescription. HQ should be applied uniformly twice daily on the affected area for at least three months and up to one year[17]. Most common adverse reactions are skin irritations (presented as skin itching, burning, stinging) and allergic dermatitis and are closely related to the applied dose as well as the duration of the treatment. Chronic use of high concentration (>5%) can cause ochronosis and colloid milium[5].

Tretinoin

Tretinoin affects the melanisation pathway by increasing epidermal turnover that decreases the contact time between keratinocytes and melanocytes[18] and disrupts melanogenesis by inhibition of tyrosinase activity[2]. Tretinoin preparations are available in concentration ranging from 0.05 to 0.1%. Tretinoin should be combined with HQ and corticosteroids[5]. It is mandatory to use UVA and UVB sun-screens while using tretinoin. The most frequent adverse events are erythema, burning, stinging, dryness, and scaling[19]. There is a risk of postinflammatory hyperpigmentation, particularly in individuals with darker skin types, therefore the dose must be adjusted to prevent inflammation[5]. Adapalene, a naphthoic acid derivative with retinoid activity, has shown similar effects on melasma with less adverse effects compared to tretinoin[20].

Azelaic acid

Azelaic acid is a naturally occurring, nonphenolic, saturated, nine-carbon dicarboxylic acid that has no effect on normally pigmented skin but only affects abnormal melanocytes[21]. The supposed mechanism of action for azelaic acid is competitive inhibition of tyrosinase[22], inhibition of reactive oxygen species and the reduction in oxydative tissue injury and melanin formation[23]. It is available in a cream at a concentration of 15 to 20% and the recommended application is twice daily. Combination of azelaic acid 20 % and tretinoin (either 0.05 or 0.1%) has better therapeutic response than azelaic acid used alone[24]. Adverse effects of the treatment include mild and transient local pruritus, burning and stinging[25]. Other adverse reactions such as erythema, dryness, rash, peeling, irritation and contact dermatitis are extremely rare.

Corticosteroids

Corticosteroids may directly affect the synthesis of melanin, although the mechanism is not fully known. Steroids may influence melanocyte function by inhibition of prostaglandin or cytokine production by epidermal cells[26] and by suppressing secretion of metabolic products from melanocytes[27]. Due to numerous adverse events, such as steroid dermatitis, allergic contact dermatitis[28], atrophic changes, teleangiectasias, corticosteroids in monotherapy are not advisable therapeutic

option. On the other hand, use of corticosteroids in combination with hydroquinone and tretinoin has proven to be successful treatment[24].

Combination therapy

Epidermal type of melasma is most successfully treated by a combination of hydroquinone, steroid and tretinoin. Kligman's formula, that was proposed in 1975 (hydroquinone 5%, tretinoin 0.1%, and dexamethasone 0.1%) has been the most widely used. Despite its effectiveness, this preparation has many side effects. Over the years new formulas have been developed with less severe side effects while maintaining or improving efficacy. The best effect was observed by the avoidance of sunlight and the use of the formulas containing low concentrations of hydroquinone and retinoid acid[1]. New formulas with less severe side effects are hydroquinone 2%, tretinoin 0.05%, betamethasone valerate 0.1%, once daily for 10 weeks or the combination of hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01% do not cause skin atrophy or thinning, rosacea or hypopigmentation[29].

Other (potential) topical agents

Kojic acid

Kojic acid, a tyrosinase inhibitor, is not approved treatment for melasma in some countries. It has been studied in combination with hydroquinone or glycolic acid in patients not responding to monotherapy with other topical agents. Efficiency of kojic acid compared to 2% hydroquinone is approximate but with more adverse reactions, such as irritation[30].

L-ascorbic-2-phosphate

L-ascorbic-2-phosphate, is a stable vitamin C derivate that supresses melanin production and may be effective in reduction of hyperpigmentation[31].

Flavonoids

Flavonoids from licorice roots (glabrene, isoliquiritigenin and liquirtin) have shown very good depigmentation effect with only mild irritation as adverse effect[32].

Physical therapies

Chemical peeling

Chemical peeling agents cause depigmentation by removing melanin. Peels are better tolerated by individuals with lighter skin, and caution is needed in darker ratial--ethnic groups because of postinflammatory hyperpigmentation and the aggravation of melasma itself. The risk of complications increases with the depth of the wound. Adverse reactions like erythema and infection are lowest with superficial chemical peels. Several peeling agents were studied like salicylic acid, trichloroacetic acid, tretinoin and resorcinol, glycolic acid peels[33] remain the most popular. Application is simple, with rare adverse reactions[33]. Glycolic acid peels at concentrations from 10 to 70% are popular and can be used in dark-skinned patients. They are usually applied once per month for 3 consecutive months. Chemical peeling can stimulate melanogenesis thus causing aggravation of disease. The use of 4% hydroquinone in a hydroalcoholic solution, 1% hydrocortisone acetate cream and 0.05% tretinoin cream after chemical peeling is recommended to inhibit the postinflammatory pigmentation, and should be used until complete regeneration of skin[15]. After the treatment the use of sunscreen is obligatory for indefinite period of time.

Other (potential) physical therapies

Dermabrasion

Dermabrasion is not standard treatment modality because of adverse reactions like postinflammatory hyperpigmentation, milia, pruritus, keloid formation, although in some studies melasma has been cleared without recurrence[2].

Intense pulsed light therapy

Intense pulsed light therapy (IPL) is an effective therapeutic choice for epidermal melasma, but long-term sun protection and bleaching creams should be used after treatment in patients with mixed melasma[34].

Laser therapy

Depending on wavelength of light emitted by laser device, light penetrates on different depth and therefore affects different type of tissue. Melanin containing structures are affected by the wavelengths over 600 nm[35]. Q-switche neodimium YAG laser[36] was not effective in the melasma treatment, as well as Q-switched ruby laser[37]. In refractory melasma the combination of CO_2 lasers and Q-switched alexandrite laser was unpredictable[38]. Erbium:YAG laser use was recommwended only for refractory melasma[39]. The pigmented lesion dye laser was ineffective in the treatment of deep dermal melasma. No single laser treatment has been effective or superior over topical agents. The use of erbium:YAG laser resurfacing does improve melasma, but because of postinflammatory hyperpigmentationis recommended only for refractory melasma.

Conclusion

Melasma should be treated using monotherapy or combination of topical therapy, mainly fixed triple or dual combinations containing hydroquinone, tretinoin, corticosteroids or azelaic acid. Modified Kligman's formula manifests as very effective. Discontinuation of the use of birth control pills, scented cosmetic products, and phototoxic drugs coupled with UV protection are obligatory measurements in combination with topical treatement. Alternative treatments including chemical peels (alone or in combination with topical therapy) seem to have the best result as an alternative to bleaching creams.

Laser treatments show limited efficacy and should rarely be used in the treatment of melasma. Combining topical agents like hydroquinone, tretinoin and a corticosteroid in addition to sun avoidance, regular use of sunscreen throughout the year and patient education is the best treatment in this difficult to treat condition.

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M. Kolić

Department of Dermatology and Venereology, »Sestre milosrdnice« University Hospital Center, Vinogradska cesta 29, 10000 Zagreb, Croatia
e-mail: majakolic.zg@gmail.com

NOVIJE SPOZNAJE U LIJEČENJU MELASME

SAŽETAK

Melasma je čest stečeni poremećaj pigmentacije koji se javlja na fotoeksponiranim mjestima, najčešće na obrazima, čelu i iznad gornje usne. Melasma se može javiti u oba spola, iako su 90% oboljelih žene. češće se javlja u osoba tamnijeg tipa kože (tip kože po Fitzpatricku IV, V i VI), pogotovo latinoamerikanci, azijati i afroamerikanci. Melasma se javlja u pubertetu ili kasnije, dok se u osoba tamnijeg tipa kože javlja već u prvom desetljeću života. Uzrok melasme još nije u potpunosti poznat, ali su poznati mnogi predisponirajući faktori. Najvažniji su ekspozicija UV zračenju i genetska predispozicija, i to u oba spola. Kod žena, uz gore navedene čimbenike, važan je i hormonalni utjecaj. Od ostalih predisponirajućih faktora ističu se stres i kozmetički proizvodi koji sadržavaju fototoksične tvari. U terapiji melasme prva linija liječenja su lokalni pripravci, u monoterapiji ili kombiniranoj terapiji, uglavnom trojna terapija, koja se sastoji od hidrokinona, tretinoina, kortikosteroida ili azelaične kiseline. Učinkovitom se pokazala i modificirana Klingmanova formula. Uz nabrojene lokalne pripravke fotoprotektivna sredstva koja štite od UVA i UVB zračenja su najučinkovitiji u liječenju epidermalnog tipa melasme. Dodatne, ali obavezne, mjere liječenja su prekid uzimanja oralnih kontraceptiva i fototoksičnih lijekova te fotozaštita. Kao druga linija liječenja primijenjuju se kemijski piling i glikolna kiselina, a nakon terapije lokalnim prirpavcima. Terapija laserom ima ograničenu učinkovitost i ne savjetuje se njegova upotreba za liječenje melasme. Kombinirani lokalni pripravci kao hidrokinon, tretinoin i kortikosteroidi, uz izbjegavanje izlaganja suncu i upotreba fotoprotektivnih sredstava svakodnevno i tijekom cijele godine te edukacija bolesnika su najbolje mjere za liječenje melasme.