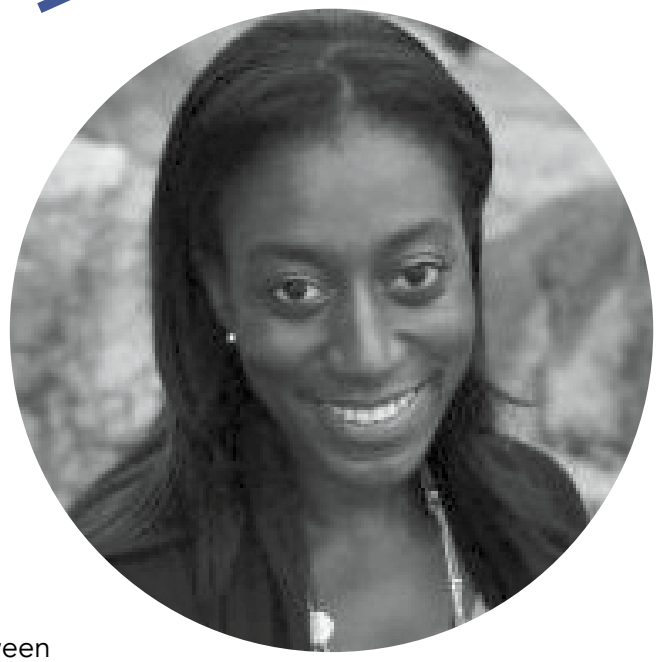
ABOUT THE AUTHOR



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AN UPDATE ON THE MANAGEMENT OF FACIAL HYPERPIGMENTATION: IS THERE ANYTHING TO USE OTHER THAN HYDROQUINONE?

The multicultural landscape of North America is changing. The visible minority population in the United States is expected to reach 50% by the year 2050.[1] Similarly, in Canada, it is projected that over the next decade, almost 1 in 3 Canadians will have Fitzpatrick skin types 4-6, with 60% of residents in Toronto and Vancouver being members of visible minority communities.[2]

Although common skin disorders such as acne and dermatitis are prevalent amongst all ethnic groups, certain conditions such as dyschromias are seen more readily in patients with darker skin. In a U.S. study comparing the top ten dermatological diagnoses between black and white patients, pigmentation disorders were the second most common reason for black patients to seek dermatological care.[3] This increased frequency of pigmentation disorders has also been observed in Asian, Latin American, African and in Afro-Caribbean communities.[4-6] Disorders of pigmentation in Caucasian patients however, were not listed in the top ten of dermatological diagnoses.[3]

There are two main types of dyschromia: melanotic and non-melanotic. Melanotic dyschromias are due to a disruption in melanocytic processes. Non-melanotic dyschromias result from other causes, such as vascular anomalies. Melanotic dyschromias can be further subdivided into disorders of hyperpigmentation and hypopigmentation.[5,7] In general, excluding vitiligo, disorders of hyperpigmentation such as melasma and post inflammatory hyperpigmentation make up the vast majority of pigmentation disorders in skin of color patients.[4] These conditions, particularly when affecting the face have been shown to decrease quality of life and cause significant psychosocial distress.[7,8] Therefore, a toolbox of effective options for treatment are essential to the practicing dermatologist.

Central to the understanding of therapeutic options for melanotic dyschromias is the complex process of skin pigmentation.[7] The steps involved are the primary targets for both traditional and emerging therapeutics. Skin pigmentation is genetically determined, however other factors such as hormonal status, exposure to ultraviolet radiation, trauma and age also play a role.[7] The steps and treatment targets in cutaneous pigmentation are outlined in **Figure 1**.[9,10]

The treatment of facial hyperpigmentation is extremely challenging, especially in patients with higher Fitzpatrick skin types. Concerns regarding the long-term efficacy, safety and cost of traditional treatments has led to the development of a variety of new and emerging alternatives for skin of color patients.[11]

1. Melanoblasts migrate from the neural crest to the dermis
2. Melanoblasts differentiate into melanocytes in the dermis
3. Melanocytes migrate to the epidermis (basal layer)
4. Mitotic division of melanocytes
5. Tyrosinase production in the rough endoplasmic reticulum and transfer to the golgi for modification
6. Formation of melanosomes with tyrosinase and tyrosinase related proteins
7. Melanogenesis (complex process of melanin production) within melanosomes
8. Transfer of melanosomes to keratinocytes
9. Eventual degradation of melanosomes within keratinocytes during differentiation

Figure 1. Stages in melanocyte development, melanosome formation and melanization, and melanin transfer to keratinocytes; adapted from Lambert et al, 2019

Disruption in specific steps leading to hyperpigmentation disorders

Melasma:
Steps:
5. Increased tyrosinase production
6. Increased melanosome formation
7. Increased melanin production
8. Increased transfer of melanosomes to keratinocytes

Post inflammatory hyperpigmentation:
Steps:
4. Increased production of melanocytes (melanocyte hyperplasia)
7. Increased melanin production
8. Increased transfer of melanosomes to keratinocytes

Steps targeted by specific treatments

Topical steroids
- Disrupt melanocyte secretory function (Step 6)

Hydroquinone, Arbutin, Licorice, Azelaic acid, Kojic acid
- Inhibition of tyrosinase (melanin production) (Step 7)

Tretinoin, Soy, Nicotinamide
- Disrupt melanosome transfer (Step 8)

Chemical peels: Glycolic acid, Salicylic acid, Trichloracetic acid, Tretinoin:
- Aid in keratinocyte removal (Steps 8-9)

Management

Behavioural Strategies:

Behavioural strategies are essential to the management of facial hyperpigmentation. Treating the underlying cause, avoidance of trauma from manipulation and/or picking the skin and camouflage make-up all play an important role in treating hyperpigmentation.[12] Avoidance of ultraviolet radiation has long been regarded as central to the management of melanotic dyschromias.[12] Visible light however, has also recently been shown to worsen facial hyperpigmentation. Protection from visible light with iron oxide containing (tinted or mineral) sunscreens has been shown to improve the appearance of hyperpigmentation.[13,14] Finally, the tincture of time is also an important concept to address with patients, especially those with post

inflammatory hyperpigmentation (PIH). Setting up the expectation that the resolution of pigmentation will take some time but is expected to fade is often encouraging for patients. In a study looking at PIH in acne, PIH resolved spontaneously in 57% of patients by 40 weeks.[15]

Topical therapies:

Hydroquinone

Hydroquinone is the gold standard topical agent for the treatment of facial hyperpigmentation. Hydroquinone is a tyrosinase inhibitor that works by preventing the production of melanin from tyrosine. The strongest evidence for its use has been in melasma at a concentration of 4%.[11] In combination with topical retinoids and corticosteroids, first popularized by Kligman,[16] its efficacy has been even higher than when it is used as monotherapy.[17] The most common side effects of hydroquinone are redness and irritation which, if they persist, can lead to the unwanted side effect of post-inflammatory hyperpigmentation. In such instances, it is best to ask the patient to discontinue its use. Another side effect of hydroquinone is the so called "hydroquinone halo."[17] This phenomenon is characterized by a rim of hypopigmentation surrounding a dark macule. These halos are thought to result from bleaching of the normal surrounding skin due to the fingertip application of hydroquinone to small pigmented macules. With prolonged use of hydroquinone, patients are at risk of the rare but significant consequence of exogenous ochronosis, or the paradoxical permanent pigmentation of the skin.[17] A number of studies have shown however, that hydroquinone can be used safely and continuously for at least six months and even up to one year without the development of ochronosis.[18-20] Beyond one year, the risk appears to be slightly increased and alternative therapies should be considered.[17]

Non-hydroquinone topical therapies for the management of hyperpigmentation

Prescription based agents:

Retinoids

Topical retinoids have been used as stand-alone therapy, and in combination with other agents to treat facial hyperpigmentation. Retinoids are vitamin A analogues which exert their effects on pigmentation in a variety of ways. Retinoids exhibit anti-inflammatory properties and modulate cell proliferation, differentiation, and apoptosis.[21] The most frequently prescribed topical retinoids are tretinoin, tazarotene and adapalene which have all demonstrated efficacy in treating facial hyperpigmentation.[22] Tretinoin is a first-generation naturally occurring metabolite of retinol. It is thought to inhibit the transcription of tyrosinase and to interrupt melanin biosynthesis. The most important effect of tretinoin in facial pigmentation is through its desquamative properties resulting in an overall reduction of melanin pigment.[15] Tazarotene and adapalene are both synthetic retinoids. In a blinded, randomized controlled study comparing the two agents in acne patients, tazorotene 0.1% cream was found to be superior in treating acne-associated PIH than adapalene 0.3% gel.[23] The main side effect of topical retinoids is retinoid dermatitis. This has been shown to occur in up to 50% of patients using these agents.[17] In skin of color patients, this is frequently associated with PIH. Minimizing this risk includes application of a moisturizing agent, slow upward titration, and selection of less irritating vehicles. Recently, tazarotene 0.045% lotion was approved for use in the United States. This new vehicle is promising as clinical trials demonstrate a reduction in skin irritation as compared to previous tazarotene formulations.[24]

Azelaic acid

Although, in Canada, azelaic acid is approved to use in rosacea, azelaic acid can also be used for melasma and PIH. Azelaic acid is a naturally occurring dicarboxylic acid obtained from cultures of *Malassezia furfur*. Azelaic acid improves hyperpigmentation by inhibiting tyrosinase.[22]

Kojic acid

Kojic acid is a metabolite of various fungal species including: *acetobacter, aspergillus* and *penicillium*. It is a potent inhibitor of tyrosinase activity and has primarily been studied in melasma. As monotherapy, it is inferior to hydroquinone in improving facial hyperpigmentation but when combined with hydroquinone and/or topical corticosteroids, its efficacy is increased.[21,25] Kojic acid is a sensitizing agent, and contact dermatitis is not uncommon.[21]

Cosmeceuticals (Non-prescription)

Licorice root extracts, soybean derived proteins, niacinamide, rucinol and ascorbic acid have all been shown to have some efficacy in the treatment of facial hyperpigmentation. For patients seeking natural formulations, any of these well-tolerated agents could be considered.[17,21,26,27]

Alternatives to hydroquinone with equivalent efficacy and fewer side effects

Topical tranexamic acid

Tranexamic acid (TA) is gaining popularity in its ability to treat facial melasma. Both topical and systemic formulations have been studied. TA is an anti-fibrinolytic agent that has been successfully used to induce hemostasis in menorrhagia and has also been used successfully to treat angioedema and urticaria through the bradykinin pathway.[28,29] TA is a synthetic derivative of the amino acid lysine and its primary mechanism of action in the treatment of hyperpigmentation is through the inhibition of UV-induced plasmin activity in keratinocytes leading to a downstream decrease in the production of prostaglandins, which are known stimulators of tyrosinase activity.[30] Split face studies comparing topical TA to traditional hydroquinone-based melasma therapies have shown equivalent strong efficacy for topical TA when compared to hydroquinone. Currently, there is no standard dosing regimen or vehicle type recommended for topical TA. A number of small studies have shown statistically equivalent success with twice daily application of cream, gel, liquid and other formulations ranging from 2 to 5%.[31] Topical TA has been reported to be well-tolerated with few and mild side effects such as erythema scale, xerosis and irritation.[30,32] Thus, topical preparations of TA represent a possible first-line alternative to the current gold standard of hydroquinone in the treatment of melasma.

Cysteamine

Cysteamine hydrochloride (beta-mercaptoethylamine hydrochloride) is a molecule that is naturally produced by the body as a breakdown product of L-cystein. Its properties of potent depigmentation have been known for more than 50 years.[33] Production of commercial products up until recently has been limited due to an offensive odour associated with topical preparations.[34] Theories on how cysteamine reduces skin pigmentation include: inhibition of tyrosinase, scavenging of dopaquione, chelation of iron and copper ions, increasing intracellular glutathione and shifting eumelanogenesis to pheomelanin synthesis.[35] The efficacy and safety profile of cysteamine has been studied quite extensively. In vitro studies have reported cysteamine to be more effective than hydroquinone.[34] In human studies, the results have also been excellent. Reported side effects include: transient irritation and a residual sulfur odour following application.[33] Thus, for patients who have recalcitrant facial hyperpigmentation, cysteamine could be considered as a viable alternative to hydroquinone.

Physical/Procedural Therapies:

Chemical peels

The use of chemical peels can be helpful in treating facial hyperpigmentation.[17] Superficial chemical peels are generally well-tolerated in darker skin types, however care must be taken to reduce the risks of irritation, dyspigmentation and scarring through selecting the appropriate agent and carefully viewing the dermatologic history. Clinical improvement in facial pigmentation with the use of chemical peels in conjunction with traditional therapies has been reported in numerous studies.[21] In addition, pre-treatment with a course of topical hydroquinone 4% is thought to improve outcomes even further.[12]

Glycolic acid (GA) is a naturally occurring alpha-hydroxy acid found in sugar cane. It decreases pigmentation primarily through epidermolysis and dispersion of melanin in the basal layer. Standard treatment protocols include application of glycolic acid 20-70%, followed by a neutralizing agent.[12,21]

Salicylic acid (SA) is a beta hydroxy acid derived from willow tree bark and induces keratolysis which aids in the removal of melanin pigmentation.

Trichloroacetic acid (TCA) and Jessner's solution have also been used to treat facial pigmentation, however evidence to support their use in skin of color is lacking.[21]

Laser and light-based therapies

Durable improvement in hyperpigmentation can be achieved with laser therapy. Careful selection of appropriate devices to avoid scarring and dyspigmentation need to be employed in patients with richly pigmented skin. The use of low fluence Q-switched Nd:YAG lasers[36] and 1927nm thulium fiber fractional lasers[37] have shown convincing results in the treatment of recalcitrant melasma. Several case reports highlighting the success of other devices have been published, however there is a need for more data to determine the efficacy and safety of these devices in skin of color patients.[12,21]

Systemic agents

Oral Tranexamic acid

As previously mentioned, TA is an anti-fibrinolytic agent. In 1979, Sadako et al discovered that oral TA could help in the management of melasma.[38] Numerous studies have been performed since that

time. The largest study to date is a retrospective study published in 2016 by Lee et al.[39] in which 561 patients were treated with oral TA at a dose of 250 mg b.i.d. Most patients were also using concurrent topical depigmenting agents.The results of this study showed that 89.7% of patients had a clinically significant improvement after two months of treatment with reported side effects including abdominal pain, bloating and headache. One patient, who was later found to have protein S deficiency, had a deep vein thrombosis six weeks into therapy. TA is currently considered a safe and effective systemic agent in the treatment of melasma, and its use should be considered in refractory cases. TA is contraindicated in patients with a history of thromboembolic disease, with the use of other anticoagulant agents, and in patients who have renal, cardiovascular or respiratory disorders, as well as those with a history of malignancy.[38] A patient's lifestyle such as pregnancy, oral contraception use and long-distance travel should also be considering prior to initiating oral TA therapy. Despite studies showing rare or minimal adverse effects, a thorough history needs to be obtained to mitigate potential risks.[38]

Parenteral Glutathione and a Word About Skin Bleaching

An article featured in the *New York Times* in 2017 exposed the controversial use of IV glutathione in medical spas and aesthetic centres across the United States for the purpose of lightening one's natural skin tone.[40] The purposeful attempt to lighten skin tone is referred to as skin bleaching and it is a global phenomenon practiced in a variety of communities throughout the world especially in parts of Asia and Africa.[41] Its use stems from the perception that lighter skin equates with beauty and higher social status. As a result, the world market for skin whitening products is expected to reach $31.2 billion by the year 2024.[42] Glutathione is a sulfhydryl-containing antioxidant compound consisting of cysteine, glycine, and glutamate.[42] It has been marketed as a safe and effective treatment for skin whitening.[40] There are several postulated theories for the skin lightening effects of glutathione including: its antioxidant properties, its ability to switch production of eumelanin to pheomelanin, its inhibition of tyrosinase and its interference in tyrosinase transfer to premelanosomes.[41] Topical, oral and parenteral formulations of glutathione exist with studies on both oral and topical glutathione formulations elucidating conflicting data mainly due to limited absorption and bioavailability.[42]

Parenteral glutathione has therefore been gaining popularity. The safety and efficacy of intravenous glutathione has not been effectively studied, and dosing guidelines have not been established. Parenteral glutathione has been associated with brain, liver and kidney toxicity, as well as Stevens-Johnson syndrome and possible malignancy.[40,41] An increased risk of blood borne infections also exists as many individuals administering these 'treatments' are not medical professionals.[40] Given the lack of the available safety data, the Food and Drug Administration in the USA and regulatory authorities in the Philippines have issued warnings on its use.[41]

Summary

A combined approach to the treatment of facial hyperpigmentation is often required **(Figure 2)**.[27] Currently, first line therapies for treating facial hyperpigmentation include: sun protection, hydroquinone and hydroquinone-containing mixtures. Several topical alternatives have been studied both in combination with hydroquinone

Behavioural strategies for all patients:
- Avoidance of picking/manipulating the skin
- Emphasize treatment of underlying cause for post inflammatory hyperpigmentation
- Camouflage make-up
- Sun/visible light protection: consider recommending broad spectrum ≥ SPF30 iron oxide containing sunscreens

1st line:
- Hydroquinone 4% (modified Kligman formulations are preferred) **stop after 6-12 months**
- Sun avoidance and sunscreen consider recommending broad spectrum ≥ SPF30 iron-oxide containing sunscreens
- Tretinoin cream

2nd line: (1st line if prior prolonged use of hydroquinone, allergy to hydroquinone or patient preference)
- Tazarotene, Adapalene, Azelaic acid
- Other cosmeceuticals (Soy, vitamin C, Licorice extracts etc)
- Chemical peels (Glycolic acid, salicylic acid, Trichloracetic acid, Jessner's solution)

3rd line:
- Topical cysteamine, topical tranexamic acid, kojic acid (warn about contact dermatitis)
- Consider oral tranexamic acid – avoid in patients with clotting disorders
- Niacinamide

Figure 2. General approach to facial hyperpigmentation[30]

and as monotherapy, with many of these having shown promising results. Procedural therapies such as chemical peels and laser devices may also be beneficial in improving facial dyschromias especially when used in combination with traditional therapies. Oral tranexamic acid is considered to be safe and effective in the treatment of facial melasma and its use should be considered in severe or difficult cases. Finally, the use of topical, oral and parenteral glutathione has not been studied enough to warrant recommendation for its use and, in addition, the promotion of glutathione for the purpose of skin bleaching brings up several ethical and safety concerns.

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