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MELASMA:

CASE SERIES AND LITERATURE REVIEW

A NOVEL MULTIMODALITY TREATMENT

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APPENDIX 1: Specimen Layout for Declaration/Statements page to be included in Taught Master's Degree Dissertations

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Abstract

Melasma often presents as a symmetrically distributed hyperpigmented facial macule. It is a condition with global prevalence and is especially common amongst younger women of darker skin tones. It is associated with sun exposure and pregnancy that results in overproduction of melanin that is retained within the skin.

The most common distribution of melasma involves the central face. Dermoscopy findings of epidermal melasma include a prominent vascular network with a pseudoreticular network of dark fine granules. The modified Melasma Area and Severity Index is the most widely used validated objective tool to track melasma progression. Although there are no associated medical complications, the visible nature of melasma significantly impacts self-esteem and overall well-being. The Melasma Quality of Life is a validated disease specific patient reported subjective assessment that evaluates the emotional state, social relationships, and daily activities of patients with melasma.

Management of melasma begins with lifestyle changes such as strict sun avoidance. Thereafter, a variety of medical and procedural interventions can be used independently or in combination with one another. Traditional and novel treatments such as tropical hydroquinone, retinoids, chemical peels, lasers, and intradermal transamin will be described in case series format in tandem with a comprehensive literature review of the selected intervention.

Successful treatment of melasma requires a patient directed multifactorial approach. Under ideal circumstances, the combination of triple combination cream, picosecond Nd:YAG, and intradermal transamin is likely to provide the greatest clinical improvement by multimodality targeting of both melasma production and elimination.

Glossary

AHA: Alpha Hydroxy Acid

BHA: Beta Hydroxy Acid

CARES: Coronavirus Aid, Relief, and Economic Security

DLQI: Dermatology Life Quality Index

Er:YAG: Erbium-doped yttrium aluminium garnet laser

FDA: US Food and Drug Administration

GA: Glycolic Acid

IL 1: Interleukin 1

MELASQoL: Melasma Quality of Life

MMASI: modified Melasma Area Severity Index

MSS: Melasma Severity Scale

Nd:YAG Neodymium-doped yttrium aluminium garnet

SPF: Sun Protection Factor

RAR: Retinoid Acid Receptor

RCT: Randomised controlled trial

TCA: Trichloroacetic Acid

TCC: Triple combination cream

TNF alpha: Tumor Necrosis Factor alpha

UVA/B: Ultraviolet A/B

VAS: Visual Analogue Scale

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INTRODUCTION

Background

Melasma is a common skin disorder that presents as symmetrically distributed areas of hyperpigmented macules. Exposed areas of the body that receive the most sunlight are at greatest risk, including the cheeks, forehead, and upper lip. Despite its widespread prevalence, it frustratingly continues to fly under the radar despite demonstrable diminished quality of life in an especially vulnerable populace of younger women of darker skin tones.
The primary author obtained his bachelor's degree at University of Toronto, Toronto, Canada before pursuing his medical degree at Northwestern University, Chicago, USA. He spent several years in surgery, with a focus in neurological surgery, and is an active member of the Royal College of Surgeons, Edinburgh, UK.

He has been in practice as a General Practitioner with a focus on aesthetic dermatology and special interest in melasma in Hong Kong, China since 2022. Patient demographics at his clinic reflect Hong Kong's multicultural melting pot with a predominance of young adult females of Han Chinese ethnicity with Fitzpatrick skin type III and IV. The significant UV radiation exposure in Hong Kong is related to an elevated risk of developing melasma. This perfect storm represents an opportunity to further explore this prevalent, relevant, and life altering condition. In addition, the diversity of treatments available for melasma fulfils the author's interest in combining medical with procedural interventions while also providing him the opportunity to employ the skills mastered during the course of his surgical training.

Epidemiology

Melasma is a very common condition affecting more than 5 million people alone in the US. It is much more common in females than males, with an accepted ratio of around 9:1. However, a large multicentre study of 953 patients found this ratio closer to 39:1. It is rare before puberty and most commonly presents during the reproductive years (20 to 40 years old) with an uptick during pregnancy. It is much more common in Fitzpatrick type III and IV skin tones, with prevalence rates greater than 10% in Latino American, Arab American, and up to 40% in females of some Asian American neighbourhoods (1).

Etiology and Pathophysiology

The pathophysiology of melasma is complex and multifactorial associated with photoaging in genetically predisposed individuals. Pigmentation ultimately results from overproduction of melanin by melanocytes and taken up by keratinocytes (epidermal melasma) or deposited in the dermis within macrophages around small, dilated vessels (dermal melasma) (1, 2).

The most important factor in the development of melasma is exposure to sunlight. People with light brown skin tone from regions of the world with intense sun exposure are much more prone to the development of melasma.

UV light induces production of free radicals via peroxidation of lipids in cellular membranes in the skin which subsequently promotes melanogenesis (1). It also induces production of alpha-melanocyte-stimulating hormone and corticotropin, as well as interleukin 1 and endothelin 1, all of which contribute to increased melanin production by intraepidermal melanocytes. Fibroblasts in the dermal layer can also contribute to melanin production via the expression of tyrosine kinase receptor c-kit and other stem cell factors (1). As such, sun protection is integral in the treatment of melasma.

Genetic predisposition is another major factor in the development of melasma with more than half of patients reporting a family history of this condition (1).

A direct relationship with female hormonal activity is believed to be present as melasma is more frequently found in females than in males and worsens during pregnancy during increases in oestrogen, progesterone, and melanocyte stimulating hormones. In addition, oral contraceptives, intrauterine devices, implants, and hormone replacement therapy are also associated with melasma (2). This is reflected by an elevation in oestrogen receptor expression in melasma lesions (1).

Thyroid disease is another medical condition that is closely related to melasma (3). Other factors implicated in the pathogenesis of melasma are ovarian dysfunction, photosensitizing medications, and certain soaps, toiletries, and cosmetics. An exogenous form of melasma known as ochronosis is known to be caused by specific medications.

History and Physical Examination

Patients generally present with progressive hyperpigmentation which may occasionally be concomitant with pregnancy, oral contraceptive use, or long-term sun exposure. The hyperpigmentation is usually bilateral tan or brown macules or patches with irregular borders. It is usually asymptomatic.

There are various patterns of distribution with the most common distribution pattern Centrofacial around the forehead, cheeks, nose, upper lip, and chin. Other distribution patterns include Malar involving only the cheeks and nose, Mandibular involving the jawline and chin, Erythosis pigmentosa faciei involving reddened or inflammed lesions, and Extrafacial involving forearms, upper arms, shoulders, in a sun exposed distribution.

Melasma can also be separated into epidermal, dermal, and mixed types. Epidermal melasma can be visualized under Wood lamp as well-circumscribed with accentuation of borders. Dermoscopy findings include prominent vascular network and a pseudoreticular network of dark fine granules. Dermal melasma findings include ill-defined borders with blue or grey discolouration and Dermoscopy findings with telangiectasias (2).

Skin biopsy is not required as melasma is primarily a clinical diagnosis but will demonstrate melanin deposition in basal and suprabasal keratinocytes, highly dendritic intensely pigmented melanocytes, melanin within dermal melanophages, solar elastosis and elastic fibre fragmentation, and increased vasculature.

The modified Melasma Area and Severity Index is one of the most popular validated tools to measure hyperpigmentation. It considers area and homogeneity across the face with a range of 0 to 24 (clear to most severe melasma). It also correlates with the Melasma Severity Score which incorporates patient assessment with rater's objective assessment. Just as importantly, the Melasma Quality of Life is a validated disease specific patient reported subjective assessment that evaluates the emotional state, social relationships, and daily activities of patients with melasma.

Differential Diagnosis

The most common differential diagnosis for melasma includes post inflammatory hyperpigmentation and solar lentigines. Post inflammatory hyperpigmentation is an excess in pigmentation due to various preceding disease processes such as inflammation, infection, allergy, trauma, and medications. It can also be due to dermatological treatment interventions such as ultrasound, radiofrequency, and lasers. Solar lentigines is a harmless patch of darkened skin secondary to chronic exposure to UV light leading to melanocyte proliferation and melanin accumulation that presents with diffuse lesions of well-defined borders.

Prognosis

There are no known medical complications associated with melasma, and it does not carry an increased risk of malignant transformation such as to melanoma or nonmelanoma skin malignancies. In fact, it is generally accepted that those with melasma are at decreased risk for melanoma due to lower rate of skin malignancies secondary to the protective effect of darker skin tones.

It is important to be aware that dissatisfaction of the appearance of melasma can affect self-image and self-esteem. This psychosocial burden can in turn lead to a decreased quality of life.

Dermal pigment may take longer to resolve than epidermal pigment. However, treatment should not be withheld simply because of a preponderance of dermal pigment. The source of the dermal pigment is the epidermis and if epidermal melanogenesis can be inhibited for long periods the dermal pigment will not replenish and will slowly resolve.

Treatment

Melasma is notoriously difficult to treat as the predominant factors that incite melasma require significant changes in lifestyle. There are texts that recommend strict sun avoidance as all wavelengths of light are capable of inducing melasma and can lead to recurrence or resistance. However, strict sun avoidance is unrealistic and incompatible with life, therefore preventative measures such as application of a broad-spectrum sunscreen SPF 50 ++++ twice a day is an essential first step in the treatment of melasma.

In addition, the pigment of melasma develops gradually and recedes at an equally slow rate. During the treatment process, it is not uncommon for patients to lose faith and give up midway. As such, the resolution to avoid instigating factors, and patience in adhering to the treatment protocol is integral to successful resolution of melasma. Fortunately, there are a growing number of methods to treat melasma. In many situations, combination treatment has been proven to be more effective than monotherapy.

Goals

This work strives to increase awareness towards a largely disregarded skin condition with global prevalence, but which also disproportionally affects the already vulnerable population of younger women with darker skin tones.

The following list of treatments was carefully curated for reasons ranging from safety, efficacy, longevity, popularity, and novelty. Each case will include a detailed discussion of each treatment and in-depth literature review.

1) Hydroquinone
2) Retinoid (tretinoin, adapalene) and Triple Combination Cream (hydroquinone 4%, tretinoin 0.05%, fluocinolone acetonide 0.01%)
3) Chemical Peels (glycolic acid, tretinoin, trichloroacetic acid)
4) Lasers (picosecond Nd:YAG, Q switched Nd:YAG, nonablative fractional laser)
5) Intradermal Transamin

Methods

Case selection was performed by retrospective chart review of all clinic patients with a diagnosis of melasma and whose most recent visit at the clinic was no earlier than 2024. This ensured that the cases were representative of patients who received the most recent interventions.

Next, to avoid pharmacodynamic interaction between interventions, only patients who received monotherapy of one of the above treatments were considered for inclusion.

Thereafter, each patient was studied to ensure the entire group was representative of the breadth of melasma both in terms of patient demographics and clinical phenotype. The group was enrolled to include differences in sex, age, skin tone, parental status, and occupation. In addition, different melasma characteristics such as new vs recalcitrant, and epidermal vs basal were also intentionally incorporated. Instead of randomisation, selective enrolment of patients was crucial to reduce the risk of variability and sampling error commonly seen in small sample sizes.

All patients were consented, and when consent could not be obtained either due to patient refusal or inability to contact patient, the process of identifying another patient who had received the same monotherapy intervention and was a good fit for the existing group was repeated.

Thereafter, each individual case was specifically designed to bring attention to the patient-tailored intervention with a detailed discussion of the associated evidence. To do this, a comprehensive literature review was performed for each treatment. The PubMed database was searched to identify recently published articles relevant to the case. High-powered papers such as randomised controlled trials or meta-analysis were given priority in the individual case discussions.

CASE ONE:

HYDROQUINONE

Introduction

Hydroquinone was one of the first few forms of treatment for melasma that has stood the test of time over the past five decades. It continues to be considered the standard depigmentation or skin lightening agent and is commonly used to treat various disorders of depigmentation including, but not limited to, melasma, solar lentigines, and post inflammatory hyperpigmentation (4). This section will focus on the use of hydroquinone in the treatment of melasma, specifically discussing its mechanism of action, methods of administration, contraindications, and possible adverse effects and complications (5).

Mechanism of action

Hydroquinone is an organic compound with the molecular formula C6H6O2 (4). It acts as a skin depigmentation agent by inhibiting melanin synthesis, specifically the conversion of L 3,4 dihydroxyphenylalanine (L-DOPA) to melanin by way of competitive reversible inhibition due to its structural similarity to an analog of melanin precursors (6).

Although hydroquinone is a poorer substrate, it is still effectively oxidized due to the production of catalytic amounts of dopa that acts as a cofactor for tyrosinase (7). The preferential oxidization of hydroquinone over tyrosinase leads to no melanin production (4).

Furthermore, hydroquinone also inhibits the distribution of melanosome dispersion throughout the dendritic projections thus limiting pigmentation uptake amongst keratinocytes (8).

Hydroquinone also has a direct effect on the cytoskeleton of melanocytes. Melanin producing cells demonstrate significant changes in their morphology after incubation with hydroquinone. They become smaller with less microtubule formation but more dendritic and clumping of cytoskeleton structures (8).

Studies have shown hydroquinone to also affect melanocyte metabolism. Cells treated with hydroquinone were found to have inhibited DNA and RNA synthesis (9). They have also been found to scavenge and trap free radicals which would in turn reduce oxidative stress and protect cellular components (10).

Methods of Administration

Hydroquinone is only used topically as a depigmentation agent. A thin layer is applied to the affected area thoroughly 1 to 2 times a day for a duration of 3 to 12 months (11). Treatment areas are generally limited to the face, decollete, and the back of hands (12).

It is generally available in 2% or 4% strength and can be found in various forms, most commonly creams, but also emulsion, gel, and solution (13). Creams containing 2-5% concentrations are considered safe and efficacious (14, 15). Around one third to half of hydroquinone is absorbed systematically after topical application (16).

It is imperative to apply hydroquinone evenly to avoid uneven pigmentation. As with all depigmentation treatments, simultaneous sun avoidance or sunscreen use is also highly recommended (6). McKesey *et al* in 2020 found that hydroquinone 3% twice a day and sunscreen daily demonstrated 96% reduction of melasma compared to 81% with hydroquinone alone (17).

Visible benefit should be seen after around 2 months of consistent use. It should be discontinued if there is no improvement after 3 months (5). After completing the treatment regimen, hydroquinone should be stopped for a few months before reinitiating treatment to reduce the risk of adverse effects. It can also be applied less frequently, such as weekends only or three times a week for extended maintenance therapy with lower risk of side effects (6).

Studies have demonstrated improved outcomes when used in combination therapy with corticosteroid and retinoid (6).

Contraindications

Contraindications include hypersensitivity to hydroquinone, persistent sun exposure, and concurrent use with other medications that exacerbate photosensitivity.

Although no studies have shown an increase in malformations or adverse effects in pregnant women, it is important to exercise caution and minimize exposure due to the substantial systemic absorption during pregnancy. It is listed Pregnancy Category C (16).

There are yet to be studies regarding its safety in breastfeeding and thus, its use should also be avoided in breastfeeding females.

Adverse Effects

Patients should be monitored for the development of side effects such as hypersensitivity (allergic or irritant contact dermatitis), hypopigmentation, post inflammatory hyperpigmentation, reduced skin elasticity, comprised wound healing, and peripheral neuropathy (4). Less common side effects include ochronosis and trimethylaminuria.

Ochronosis is a blue black/grey discolouration secondary to the use of concentrated hydroquinone for an extended duration leading to homogentisic acid accumulation and deposition in the skin. The most accepted theory suggests that the hyperpigmentation is associated with local competitive inhibition of the enzyme homogentisic oxidase by hydroquinone which leads to local accumulation of homogentisic acid and its metabolic products that polymerizes to form ochronotic pigment in the papillary dermis. (18, 19).

Exogenous ochronosis begins with erythema and mild pigmentation change, followed by hyperpigmentation, black colloid milia, and atrophy, culminating in the development of papulonodules (20, 21). lesions are gray-brown or blue-black macules with hyperchromic, pinpoint, and caviar-like papules (22).

Dermoscopy may identify dark brown globules on a diffuse brown background compared to the fine brown reticular pattern on a faint light brown background in melasma. However, due to common over the counter or prescription hydroquinone use, both conditions frequently co-exist. Histopathology is the gold standard and will demonstrate pathognomic feature of ochre-coloured banana-shaped fibres in the dermis.

The medication should be stopped in these cases. Ochrnosis is considered permanent, but dermabrasion and laser have had some success in improving the condition (23, 24).

Trimethylaminuria is a condition where a rotten fish odour is secreted in sweat, urine, and saliva due to chronic hydroquinone use (23). It is also known as “fish odour syndrome”. This is believed to be secondary to hydroquinone’s antioxidant properties that prevents the oxidation of trimethylamine.

Although there have been concerns regarding its carcinogenicity, there have been no studies yet able to determine a causal relationship between the use of hydroquinone and an elevated risk of malignancy (25, 26, 27). Regardless, hydroquinone is not approved for over-the-counter use in USA and is also banned in various countries such as Japan, Australia, and the EU (4).

A multidisciplinary interprofessional health care team approach should be utilized to ensure that patients achieve maximum benefit while reducing the incidence of adverse events. This can include regular short interval follow up with nurses to evaluate for adverse events and medication reconciliation with pharmacists to reduce the risk of hyper photosensitivity.

Case Presentation

A was a 40 year old Chinese woman Fitzpatrick III who first presented in late 2023. She was concerned with the gradual development of freckles along the superior lateral cheeks over the past few years.

Past medical and surgical history were unremarkable. She was a mother of three kids, with her youngest age 3. She denied ongoing pregnancy or menopausal symptoms. She suspected that her freckles might have developed around the same period as her most recent pregnancy.

She denied any ongoing or recent medication use, specifically oral contraceptives or other hormonal products.

There was no family history of hyperpigmentation.

She denied tobacco, alcohol, and drugs. She endorsed regular sunscreen use and biweekly trips to her aesthetician for moisturizing facials.

Review of systems was unremarkable, specifically for endocrine dysfunction.

Examination demonstrated a symmetrical concentration of numerous macular brownish hyperpigmentation over the bilateral superior lateral cheeks. This area was around 2 x 2 cm on both sides. There were no other hyperpigmented lesions identified in the face, neck, or hands.

Woods lamp demonstrated well circumscribed and accentuated borders suggestive of epidermal and dermal pigmentation. Dermoscopy demonstrated prominent vascular network and a pseudoreticular network of multiple brown dots.

A was diagnosed with mild melasma.

The validated modified Melasma Area Severity Index and Melasma Severity Scale was utilized to objectively determine the extent of facial hyperpigmentation. Her modified Melasma Area and Severity Index was 3.2. And her Melasma Severity Scale was mild.

She received disease counselling and was recommended to use sunscreen twice a day with a SPF of 50 and PA of ++++ to ensure optimal UVA and UVB protection.

Various treatment options were discussed including medical (topical and oral) and procedural (chemical peels, lasers, injectables). She agreed to start conservatively with hydroquinone 4% daily on the affected areas with follow up in 1 month.

At 1 month follow up she demonstrated visible improvement in her melasma. She too was very pleased with the change. Her mMASI was down to 2.4. She denied any side effects such as hypersensitivity, irritation, or hyperpigmentation.

At 2 month follow up her condition demonstrated further, but minimal improvement. She endorsed medication compliance and although disappointed, was also satisfied and acknowledged that a complete resolution of hyperpigmentation is unlikely. Her mMASI was 1.6.

At 3 month follow up her condition remained stable. She was recommended to reduce dosing to three times a week to decrease the risk of possible side effects.

At 6 month follow up her condition remained stable.

Her most recent follow up was in December 2024 where her melasma has remained stable on hydroquinone 4% three times a week. She was reminded of the importance of sunscreen, the possible side effects of hydroquinone, and there was discussion to transition to an alternative treatment. At that time, she was settled and comfortable with hydroquinone 4% and requested reassessment in 3 months.

Discussion

Hydroquinone cream is commonly used in the treatment of melasma. A PubMed database search was performed with the key terms “melasma” and “hydroquinone” to identify research related to the use of hydroquinone in the treatment of melasma. Given the wealth of literature regarding hydroquinone in the treatment of melasma dating back to half a century ago, the discussion will focus on several recently published higher-powered publications including systematic reviews and meta-analysis of randomized controlled trials published in reputable journals. Several primary studies that compared hydroquinone with the growing abundance of other medications and modalities for the treatment of melasma were also included as a segue into the next few case presentations.

Rajaratnam *et al* from Birmingham published a systematic review in the Cochrane Database in 2014 including all randomized controlled trials that evaluated topical and systemic interventions for melasma. They included a total of 20 studies of 2125 participants undergoing 23 different treatments and found that hydroquinone 4% was superior to 2% at lightening melasma. They also found that triple combination therapy of hydroquinone, tretinoin, and fluocinolone acetonide was superior to dual therapy or monotherapy hydroquinone. Notably, the studies did not always use validated scoring systems and were also insufficient in terms of studying the duration of response (28).

Austin *et al* subsequently performed another systematic review of topical treatments for melasma in 2019. Similar to Rajaratnam *et al*, only randomized controlled trials were included. 35 studies were included with similar findings compared to the previous study; triple combination agents demonstrated superior outcomes in the treatment of melasma (29).

Mckesey *et al* performed yet another systematic review regarding melasma treatment in 2020. This time the authors considered only the most recent randomized controlled trials dating from 2018. They included a total of 113 studies and again found similar results where triple combination cream (hydroquinone, tretinoin, and corticosteroid) was the most effective treatment for melasma. Interestingly, they found monotherapy hydroquinone to be equally effective. Unfortunately, the pre-existing literature continues to lack sufficient long term follow up (17).

Liu *et al* from Beijing published a meta-analysis in 2021 comparing the efficacy of various melasma treatments. In this meta-analysis, 59 randomized controlled trials were included. Surprisingly, they found that Q switched Nd:Yag 1064nm laser was superior to triple combination cream. In fact, intense pulsed light and ablative fractional laser also had superior efficacy. However, these procedural interventions were also found to be associated with a higher likelihood of side effects. Taking into consideration both efficacy and safety, triple combination cream was still considered to be most favourable intervention for melasma. In addition, 87% of studies demonstrated that combination therapies were superior to single therapy. The quality of evidence studied in this meta-analysis is particularly strong because nearly 50% of studies were split-face RCTs (30).

Chang *et al* from Harvard published the most recent meta-analysis in 2023 comparing the efficacy and safety of topical agents in the treatment of melasma. They included original studies that reported pre and post treatment Melasma Area Severity Index/modified Melasma Area Severity Index. The main outcome was the change in index score pre and post treatment. 45 studies of 2359 patients met the inclusion criteria. Hydroquinone monotherapy, triple combination cream therapy, cysteamine, tranexamic acid, and azelaic acid all demonstrated significant and comparable efficacy of a standardized mean difference of –1.3 to –2.0. This corroborates with case study A who had demonstrated an improvement of –1.6. The study also identified that the patients who underwent triple combination cream therapy or cysteamine had the greatest adverse events whereas the patients who underwent tranexamic acid had the least adverse events (31).

Albzea *et al* from the Middle East also published a meta-analysis in 2023 comparing the efficacy of hydroquinone and azelaic acid specifically. 6 studies were included with a total of 673 patients with the majority based out of the Middle East. They found that azelaic acid outperformed hydroquinone in terms of improving MASI scores with no significant differences in adverse events. However, the studies included were of relative smaller sample size. More primary research with bigger sample size and longer follow up would be ideal to further evaluate the utility of azelaic acid in melasma (32).

Lima *et al* from Brazil also compared the use of hydroquinone and cysteamine in a randomized controlled study in 2020. This multicentre evaluator blinded trial of 40 women was dosed nightly. Hydroquinone outperformed cysteamine in reducing mMASI scores at 60 (41% vs 24%) and 120 (53% vs 38%) days. There were no differences in side effects (33).

Gheisari *et al* from Iran compared the use of hydroquinone and methimazole in a randomized controlled study in 2020. This was a double blinded trial with 40 patients who completed the entire study duration of 12 weeks. The patients were treated nightly for 8 weeks. Both groups achieved significant improvement in MASI score by the 4th week with hydroquinone outperforming methimazole significantly. However, both groups had a significant increase in MASI score at 12 weeks after the treatment had been stopped in the 8th week. However, MASI scores remained significantly improved from baseline with hydroquinone still demonstrating superiority suggesting at least some short-term retention of treatment benefit of hydroquinone (34).

No doubt the most feared complication to both the patient and practitioner in the use of hydroquinone for melasma is exogenous ochronosis because it not only worsens the original condition, but even more so because its treatment is challenging and generally unsuccessful. The FDA enforced the 2020 CARES Act and Over The Counter Drug Monograph Reform stating that hydroquinone is not classified as Category II/not generally recognized as safe and effective (GRASE) and prohibited the distribution of OTC hydroquinone products (35, 36). It is also banned in EU, Australia, and Japan (1). Nevertheless, it remains reportedly easy to procure in the UK (37).

Ishack *et al* performed a systematic review of exogenous ochronosis associated with hydroquinone use in 2021. They identified 57 articles with 126 patients suffering from hydroquinone associated ochronosis. The demographics were predominantly female, black or asian, african or chinese, Fitzpatrick V and VI, and undergoing treatment for hyperpigmentation or melasma (20).

In the majority of cases, the concentration of hydroquinone was either greater than 4% (35.7%) or unknown (32.5%). Ochronosis associated with hydroquinone concentrations of 4% or less than 4% made up 16.7% and 15.1% respectively. The median duration of use was 5 years, ranging from 2 months to 30 years, with the vast majority (82.5%) occurring in patients who have applied hydroquinone for more than 1 year, with many greater than 4 years (71.4%). There were only four cases reported to have applied hydroquinone for 3 months or less (3.2%). These finding suggests that hydroquinone concentrations above 4% and longer than 3 months may be associated with new onset exogenous ochronosis (20).

Conclusion

Melasma is a dermatological condition that afflicts a global demographic, and this is reflected in its strong research interests throughout the world. It is no doubt that case study A benefited from our treatment of hydroquinone 4% to a level as predicted by the literature.

Triple combination cream might produce superior outcomes with no increased side effects. In addition, there is a growing number of alternative treatments ranging from topical creams to procedural lasers that have demonstrated similar or even superior outcomes compared to the long standing first line hydroquinone.

Exogenous ochronosis is a real and challenging complication that can occur at any point of hydroquinone use. The risk tends to increase relative to concentration and duration of drug application.

Patients on hydroquinone should take breaks off the medication to reduce the risk of exogenous ochronosis. There should still be improvement in clinical condition during this period as hydroquinone has proven to retain its efficacy at least 4 weeks after therapy cessation. It is worth considering transitioning these patients to triple combination cream due to its superior outcomes.

CASE TWO

RETINOIDS

TRETINOIN AND ADAPALENE

TRIPLE COMBINATION CREAM

Introduction

Retinoids have been used in the treatment of pigmentary disorders such as melasma, solar lentigines, and post inflammatory hyperpigmentation (38). Its use in the treatment of melasma dates to the 20th century (39). This section will focus on the use of topical retinoids in the treatment of melasma, and will discuss its mechanism of action, methods of administration, contraindications, and possible adverse effects and complications.

Mechanism of action

Retinoids are a class of chemical compounds derived from Retinol (Vitamin A). Retinol is a 20-carbon molecule that consists of a cyclohexenyl ring, a side chain with four double bonds (all in trans configuration), and an alcohol end group, hence the name all-trans-retinol (40).

Oxidation of the alcohol end group results in the formation of an aldehyde, and further oxidation will subsequently produce carboxylic acid which provides the basic structure of the hydrophobic retinoid molecule; a cyclic end group, a polyene side chain, and a polar end group. Further alternation of side chains and end groups creates the various classes and generations of retinoids (41).

Retinol undergoes this oxidative process via biological enzymes to influence a vast number of biological processes beyond the skin. They are also involved in vision, immune function, and reproduction (40, 42, 43, 44).

Retinoids mediate their effects by binding to cellular receptors, specifically Cellular Retinol Binding Protein and Cellular Retinoic Acid Binding Protein (CRABP) types I and II. Thereafter, they are transported into the nucleus where they bind to nuclear receptors, Retinoic Acid Receptor (RAR) and Retinoid X Receptors (RXR). These receptors form a heterodimer that subsequently binds to specific elements in the DNA known as the Retinoic Acid Response Elements (RARE) and regulates transcription activity related to increasing keratinocyte turnover and decreasing melanocyte activity. In addition, retinoids are also believed to increase epidermal permeability, thereby facilitating the penetration of adjunct therapies (40).

Tretinoin continues to be considered the gold standard amongst retinoids used in the treatment of hyperpigmentation. However, the discovery of the retinoid pathway has led to the development of newer targeted treatments, such as the third generation retinoid Adapalene that acts selectively on RAR-β (40).

Tretinoin alone is FDA approved for adjunctive palliative treatment of photoaging such as fine facial wrinkles, facial skin roughness, and facial mottled hyperpigmentation. Whereas tretinoin 0.05%, in combination with hydroquinone 4% and fluocinolone acetonide 0.01% is the only topical ointment approved by the FDA in the treatment of melasma.

Methods of Administration

Topical tretinoin cream, gel, and ointments are applied topically as a depigmentation agent. Dosages vary across different brands with the standard topical tretinoin available between 0.04% - 0.1%.

A thin layer is applied once daily before bedtime to the affected area thoroughly. It is recommended to avoid the eyes, mouth, nasal creases, and mucous membranes (45).

Treatment response is slow, and a treatment duration of at least 6 months is expected before significant improvement can be visualized (46).

Patients with sensitive skin might experience skin pain, erythema, and pruritus. The treatment frequency can be adjusted as tolerated. Patients who are still unable to tolerate tretinoin can consider newer generation selectively acting retinoids such as Adapalene which has a more tolerable profile.

Over the past decade, there have been increasing research into advancing retinoid delivery by optimizing efficacy and minimizing side effects. In animal studies, the use of solid lipid nanoparticles has improved physical stability, localization, and tolerability whereas inorganic nanoparticles have even demonstrated clinical improvement in skin wrinkling and texture (47, 48).

In addition, because of its ability to increase epidermal permeability, there is a wealth of literature demonstrating improved outcomes in the treatment of melasma when used in combination with other depigmentation agents (49).

Contraindications

Contraindications include hypersensitivity to tretinoin and 1st trimester pregnancy. Caution is also recommended if there is a history of hypersensitivity to fish products and sunburn/photosensitivity.

Tretinoin is a known teratogen and is classified as Pregnancy Category C (45).

Of note, there has been no reported teratogenicity related to topical tretinoin use in the literature. In a case control study of 215 mothers exposed to topical tretinoin in the first trimester, the prevalence of major fetal malformations was 1.9% and 2.6% in the tretinoin and control group respectively (50).

However, it is still prudent to advise women to avoid pregnancy and discontinue treatment during pregnancy to avoid the unwanted possibility of fetal loss and malformation (51).

Adverse Effects

The most common adverse effects in topically administered tretinoin are known as “retinoid reaction”, characterized by pruritus, pain, erythema, and peeling. This is due to the free carboxylic acid in the polar end of the retinoid stimulating the release of proinflammatory cytokines IL1 and TNF alpha (52).

This generally presents within the first few weeks of treatment, and the dose/frequency should be adjusted accordingly. The addition of a corticosteroid can be considered to both relieve the side effects and as an adjunct therapy alongside tretinoin to further reduce the melasma (53).

Another common side effect is photosensitization which generally occurs at the beginning of therapy. The skin response to UV radiation gradually returns to normal over a few months. To best manage this, only apply tretinoin before bedtime and apply sunscreen or practice sun avoidance during the day. Sun avoidance or sunscreen use is especially important alongside retinoids because they increase epidermal permeability and reduce the skin's innate defence mechanism against UVA and UVB.

Other less common adverse effects include subcutaneous irritation, pharyngitis, and irritant conjunctivitis when tretinoin is applied close to the eye (53).

Topical tretinoin has not been found to have a detectable effect on endogenous plasma levels of tretinoin or its metabolites (54). As such, there has been no reported systemic side effects of topical retinoids for long term treatment of melasma. However, it is still important to be aware of the signs of Vitamin A toxicity, such as headache, nausea/vomiting, bone pain, skin/mucous membrane dryness, and visual disturbances (45).

A multidisciplinary interprofessional health care team approach should be utilized to ensure that patients achieve maximum benefit while reducing the incidence of adverse events. This can include regular short interval follow up with nurses to evaluate for adverse events and medication reconciliation with pharmacists to reduce the risk of hyper photosensitivity.

Case Presentation

B was a 55 year old Chinese woman Fitzpatrick IV who presented in mid 2024 with concerns of bilateral cheek hyperpigmentation over the past few years.

She was mildly obese but otherwise reported that she was endorsed with a clean bill of health at her annual body check. She denied any past medical and surgical history. She was postmenopausal and denied any history of pregnancy and childbirth.

She reported having used a "whitening cream" shared with her by a distant relative for almost a year but has since stopped a few months ago because she was concerned that the pigmentation was worsening. She no longer had the cream nor was aware of its ingredients. She denied any other medication use, specifically oral contraceptives or other hormonal products.

There was no family history of hyperpigmentation.

She denied tobacco, alcohol, or drug use. She worked as a nail aesthetician. She denied frequent sun exposure or sunscreen use. She used a facial cleanser and sunscreen twice a day.

Review of systems was unremarkable, specifically for endocrine dysfunction.

Examination demonstrated a mostly symmetrical macular brownish hyperpigmentation diffusely spread over the bilateral cheeks. This area was around 5 x 5 cm on both sides. There was a darker and concentrated bluish black patch along the right inferolateral peri-orbital area. There were no papules or milia. In addition, similar macular brownish hyperpigmentation was identified across the back of her hands. No other hyperpigmented lesions were identified in the neck.

The macular brownish hyperpigmentation over the face and back of hands were found under Woods lamp to have well circumscribed and accentuated borders suggestive of epidermal pigmentation and demonstrated prominent vascular network and a pseudoreticular network of multiple brown dots under dermoscopy. However, the bluish black hyperpigmentation delivered slightly different findings under the dermoscope with velvety areas of scattered blue grey dots and globules with a caviar like appearance.

B was diagnosed with moderate melasma and Dogliotti Stage II Exogenous Ochronosis of the right inferolateral periorbital area (55).

The validated modified Melasma Area Severity Index and Melasma Severity Scale was used to objectively determine the extent of facial hyperpigmentation. Her modified Melasma Area and Severity Index was 7.2. And her Melasma Severity Scale was moderate-severe.

She was counselled on both melasma and exogenous ochronosis, and instructed to avoid further use of any depigmentation cream that might contain hydroquinone. She was also instructed to apply sunscreen daily to her face, neck, and hands to reduce the risk of occupational skin disease.

Contrary to beliefs, nail aestheticians are exposed to a significant amount of ultraviolet radiation despite working an indoor job because of the nail lamps (56). Sunscreen with a SPF of 50 and PA of ++++ is required to ensure optimal UVA and UVB protection.

She requested topical treatment and specifically declined any procedural (chemical peels, lasers, injectables) interventions. Given her history of exogenous ochronosis, she was prescribed with Tretinoin 0.1% nightly on the affected areas with follow up in 1 month.

She returned after 2 weeks with complaints about skin burning, itching, and erythema. She was transitioned to Adapalene 0.1% to reduce retinoid reaction.

At 1 month follow up there was no improvement in melasma. She endorsed drug tolerability and compliance and was reminded that retinoid monotherapy requires a significant amount of time and dedication before visible improvement.

At 6 month follow up she felt her condition had demonstrated improvement. Her mMASI was 4.8. Although there was no significant change in her left inferolateral periorbital hyperpigmentation she is pleased with the generalized improvement of her skin. She was offered procedural interventions for exogenous ochronosis but preferred to revisit this at a later stage.

Discussion

Retinoids are most commonly used in dermatology in the treatment of acne vulgaris. However, they are also used off label in numerous other skin conditions including pigmentary disorders such as melasma, solar lentigines, and post inflammatory hyperpigmentation. A pubmed database search with the key terms “melasma retinoid”, “melasma tretinoin”, and “melasma adapalene” was used to identify research related to the use of topical retinoids, in particular the most researched tretinoin and the RAR-β selective Adapalene.

In addition to standalone retinoid therapy, triple combination cream will also be discussed because of retinoid’s essential ability to increase epidermal permeability and increase efficacy of adjunctive treatment.

One of the earliest randomized controlled studies involving tretinoin monotherapy in the treatment of melasma was performed by Griffiths *et al* in 1993. 38 Caucasian women were randomized into two groups of either 0.1% tretinoin or cream daily for 40 weeks. Significant improvement in the tretinoin group was first recorded after 24 weeks. Improvement was defined clinically, colorimetry, and histologically. These findings have stood the test of time in that tretinoin produces significant clinical improvement but only after a lengthy treatment duration. Of note, moderate cutaneous side effects occurred in 88% of the tretinoin group vs 29% in the control group (46).

Shortly thereafter, the same team at Michigan replicated a similar study design but in African American subjects. This time, they increased objectivity by utilizing the gold standard MASI score in addition to their colorimetric and histologic findings. They reported 32% improvement in MASI in the treatment group compared to the control group after 40 weeks of intervention. This correlated with improvements in colorimetric and histologic findings. They also noted a mild “retinoid dermatitis” in 67% of tretinoin treated subjects (57).

These randomized studies with respectable sample size suggest that consistent use of topical tretinoin over the course of at least 6 months reduces melasma hyperpigmentation. However, these two studies do not adequately represent case study B due to differences in Fitzpatrick skin type.

Fortunately, Leenutaphong *et al* out of Thailand again replicated the study design, this time in Oriental skin tones in 1999. There was another minor change in this study in which the authors decided to use isotretinoin gel 0.05% in a broad-spectrum sunscreen vehicle base instead of tretinoin. 30 subjects with moderate to severe melasma demonstrated an average MASI reduction of 68.2% in the treatment group vs 60% in the control group. There was a significant reduction in MASI score compared to baseline, but no significant difference was noted between both groups. This improvement was first observed at 4 weeks and lasted the duration of the 40-week study. "Retinoid dermatitis" presented in 27% of isotretinoin subjects. These findings suggested that sunscreen, and not isotretinoin, had a significant effect on lightening melasma (58).

This study group was an ideal representation of case study B who was also Fitzpatrick Type IV with moderate to severe melasma. Although no significant improvement was noted with isotretinoin, isotretinoin might not have similar efficacy compared with tretinoin in the treatment of melasma. Of note, case study B had been counselled about sunscreen compliance which had a demonstrable effect in the treatment of melasma in this study.

Dogra *et al* in 2002 studied the use of Adapalene in melasma due to its improved tolerability compared to tretinoin in the treatment of acne vulgaris. 30 Indian females were randomized to either tretinoin 0.05% or adapalene 0.1%. There was a significant reduction of MASI scores at 14 weeks compared to baseline, 37% in the tretinoin group and 41% in the adapalene group. There was no significant difference between these two groups. However, side effects were significantly less in the adapalene group 13% vs 63%. These findings suggest that adapalene is non-inferior to tretinoin in the treatment of melasma with the benefit of fewer adverse events (59). This was also witnessed in case study B's increased tolerance after transition to Adapalene.

These early studies provide a platform for future research that can consider larger sample size, utilization of split-face application, and double-blinding of both subjects and investigators to further strengthen the evidence regarding the use of retinoids in the treatment of melasma.

A review of the role of topical retinoids in the treatment of pigmentary disorders was performed by Kang *et al* in 2009. They included a total of 13 articles that studied the use of retinoids in the treatment of melasma and concluded that there was evidence to support the use of topical tretinoin as monotherapy in the treatment of melasma (grade B) and also the use of topical tretinoin as part of a fixed triple combination therapy (hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%) in the treatment of melasma (grade B) (38).

Retinoids have demonstrated efficacy in the treatment of melasma as a standalone agent and further increase the potency of adjunct depigmenting agents such as when used as part of a fixed triple combination cream of hydroquinone, tretinoin, and fluocinolone acetonide. This is believed to be due to its primary function of stimulating epidermal keratinocyte turnover which in turn decreases melanosome transfer and accelerates melanin loss via epidermopoiesis and its secondary ability to alter the stratum corneum and increase permeability thereby facilitating the penetration of depigmenting agents into the epidermis thus increasing bioavailability leading to greater depigmentation (60).

Torok in 2006 published a review article regarding the long- and short-term treatment of melasma with the triple combination cream. A total of over 2000 subjects Fitzpatrick type I to IV with moderate to severe melasma were treated, some for longer than 1 year. There was significant improvement within 2 months that lasted well beyond 1 year. The most severe adverse events were 2 incidences of skin atrophy and there were no reported cases of exogenous ochronosis (61).

The largest trial within this review was PIGMENT (Prospective Investigation Gauging Melasma Reduction with a New Treatment), a phase IV community-based trial involving 393 investigators throughout the US including 1042 subjects of all Fitzpatrick types. MASI score was significantly reduced at week 4 for all Fitzpatrick types compared to baseline. There were 8 incidences of telangiectasias and no cases of skin atrophy or other serious adverse events. In addition to objective outcomes, a health questionnaire to evaluate the impact of quality of life was also utilized with subjects feeling less self-conscious and less unattractive compared to baseline (62).

This large community-based trial provides strong evidence that the triple combination therapy cream improves both objective and subjective outcomes in all racial groups with moderate to severe melasma with low incidence of adverse events.

A meta-analysis of randomized controlled trials comparing the efficacy of melasma treatment was performed in 2021. 59 studies were included with triple combination cream the most efficacious amongst the non-procedural interventions and the most favourable selection among topical drugs for melasma. In addition, 87% of studies demonstrated that combination therapies were superior to single therapy. The quality of evidence studied in this meta-analysis is particularly strong because nearly 50% of studies were split-face RCTs (63).

Conclusion

Melasma is a dermatological condition that affects all races and skin types. It might not be a life or death scenario but can have severe consequences on an individual's self-esteem and quality of life (62). The latest and best research addresses the condition in all skin types in both objective and subjective measures.

Topical retinoids are most frequently used in the treatment of acne but have also been found to be efficacious in the treatment of melasma. Understanding their mechanism of action has not only led to the development of synthetic newer generation retinoids that act selectively on cellular receptors leading to increased tolerability due to reduced adverse effects and also led to its use in a triple combination cream in order to take advantage of its ability to increase epidermal permeability and increase bioavailability of adjunct therapies.

At this time, triple combination cream composing of hydroquinone, tretinoin, and flucinolone acetonide is the only FDA approved treatment for melasma and has demonstrated its efficacy and safety in numerous large sample size trials consisting of subjects of all skin types. However, advances in understanding the retinoic acid pathway continues to make headway and is evidenced by the recent creation of the fourth generation trifarotene with even greater selectivity to RAR (41).

Patients on retinoids can be assessed for transition to the equally safe but more efficacious triple combination cream. In addition, procedural interventions such as microneedling and lasers may have beneficial effect in the treatment of exogenous ochronosis.

CASE THREE

CHEMICAL PEELS

GLYCOLIC ACID, TRICHLOROACETIC ACID

Introduction

Chemical peels are used in the treatment of a variety of dermatological conditions. These range from epidermal growths (seborrheic keratosis, warts, milia), inflammatory conditions (rosacea), and the correction of skin colour and texture (hyperpigmentation, scars, wrinkles, and pores) (64).
Chemical peels are either alcohols that contain a carboxyl (-COOH) and hydroxyl (-OH) groups or regular acids. They can be classified metabolic, caustic, or toxic, based on their chemical properties.

There are numerous categories of peels that are used in the treatment of melasma including but not limited to Alpha Hydroxy Acid (AHA) such as Glycolic Acid and Mandelic Acid, Beta Hydroxy Acid (BHA) such as Salicylic Acid, and Trichloroacetic Acid (65).

Chemical peels are generally advertised based on their pH. However, the free acid available (pKA; pH at which half the acid is in acid form) is a more accurate determinant of strength. Different agents and formulations can be selected based on desired depth of penetration and risk profile.

This section will focus on the use of chemical peels in the treatment of melasma, and will discuss their mechanism of action, methods of administration, contraindications, and possible adverse effects and complications.

Mechanism of action

Chemical peeling, also known as chemexfoliation, utilizes caustic agents that induce accelerated exfoliation. This controlled damage releases cytokines and inflammatory mediators which results in epidermal thickening, collagen deposition, structural reorganization, and dermal volumization (64).

Superficial peels penetrate the epidermis, medium peels penetrate the papillary dermis, and deep peels extend down into the reticular dermis.

Weaker agents such as AHAs and BHAs induce rejuvenation activity via metabolic or caustic effect.

AHAs such as Glycolic Acid (GA) and Mandelic Acid reduce sulphate and phosphate groups from corneocytes, decreasing cohesion, and inducing exfoliation. Changes in pH lead to cellular swelling and transient increase in cell matrix size. At higher concentrations, these changes can also lead to superficial shock, cell injury, and death. BHAs such as Salicylic Acid is lipid soluble and has additional anti-inflammatory and anaesthetic effects. This results in improved tolerance secondary to decreased amount of erythema and discomfort commonly associated with chemical peels (64).

On the other hand, stronger agents such as Trichloroacetic Acid (TCA) can produce a chemical necrosis of the skin. TCA can be used to create superficial, medium, or deep peels. TCA is generally safe from 10-35% but at higher concentrations (>50%) has a tendency to scar and is less manageable than the abovementioned peels (64).

Destruction confined to the epidermis results in rapid healing without scarring but with less dramatic results compared to deeper penetration into the reticular dermis. Epidermal changes are visible within 2 weeks whereas dermal regeneration is a slower process that takes place across a few months. These changes result in an improved clinical appearance with fewer rhytids and reduced pigmentary dyschromia (64).

This controlled epidermal dyscohesion and subsequent regeneration has a beneficial effect on both epidermal and dermal melasma. The superficial effects remove epidermal melanin and halts melanosome transfer to keratinocytes. The dermal component occurs secondary to induced phagocytosis of stagnant melanin (65).

Methods of Administration

Prior to application of the chemical peel, priming of the skin is recommended to ensure uniform penetration of the reagent for best results and reduced risk of complications (66).

The gold standard for priming is hydroquinone 2-4% for 4 weeks. This is withheld the day before and after chemical peeling. The primer should be continued for 3 months as maintenance. Other priming agents such as retinoids (tretinoin, adapalene) or GA 6-12% follow a similar schedule. The peel itself is best applied every 2 to 4 weeks (65).

It is important to ensure patient compliance and manage expectations, including counselling the patient regarding the possibility of cosmetically unattractive skin during exfoliation.

Prior to application of the chemical peel, the patient is positioned supine, and the face is cleansed with isopropyl alcohol. The eyes should remain closed and occlusive ointment is applied to the lips. A gauze is used to apply the peeling agent to the patient. The duration of application and number of coats can be titrated according to patient tolerance. Certain agents illicit a change in skin colouration to a whitish tint known as frost. This represents keratin agglutination and signals completion of the chemical reaction.

AHA must be neutralized using water or a weak buffer as their weak acidity does not induce sufficient coagulation of skin proteins. BHA endpoint is visible by the formation of pseudofrost when the salicylic acid crystalizes. TCA produces frosting and requires a neutralizing agent or cold water starting from the eyelids (64).

Contraindications

Contraindications include open wounds, active infection, inflammatory dermatoses (psoriasis, atopic dermatitis, pemphigus), abnormal scarring (hypertrophic or keloid scars), and drugs with photosensitizing potential. Uncooperative or unrealistic patient expectations should also be considered an absolute contraindication due to the risks for self-inflicted injury during the recovery process (64, 65).

Adverse Effects

The main factors that affect adverse effects include type of chemical, concentration, number of coats, and duration of application (66).

Adverse events can be classified according to their timeline. Intraprocedural adverse events are commonly due to incorrect peel pharmacology and accidental solution misplacement while post procedure adverse events can be related to poor postprocedural care (67).

These adverse events can present immediately or delayed. Immediate complications include irritation, burning, pruritus, pain, erythema, oedema, and blistering. These symptoms can be addressed with ice application, calamine lotion, topical steroids, and emollients (68).

Delayed complications present as infections, scarring, poor healing, milia, acneiform eruptions, hyperpigmentation, and hypopigmentation (69).

Infected wounds should be swabbed for culture and treated with the appropriate topical and oral antibiotics/fungals. Wound cleaning with potassium permanganate and light debridement can facilitate healing. Peels are also known to cause reactivation of herpes simplex which can be addressed with an oral or topical antiviral agent (68).

Hypo and hyperpigmentation are more common in Fitzpatrick type III to VI and should be treated with a combination of hydroquinone, retinoic acid, and hydrocortisone once re-epithelization is complete (68).

The best form of treatment is prevention as such careful patient selection is integral to reduce the risks of adverse events. Chemical peels are most suitable for Fitzpatrick type I to III individuals who are at lower risk for pigment dyschromia and scarring. In addition, patient compliance is required to prime the skin, use broad spectrum sunscreens, and avoid skin picking during the post procedure period.

Glogau photoaging classification also recommends that deep peeling be used primarily in type 4 patients (deep static wrinkles and yellow-gray discolouration of skin) as it may be more damaging than beneficial in type 1 patients (mild early photoaging) (64).

A multidisciplinary interprofessional health care team approach should be utilized to ensure that patients achieve maximum benefit while reducing the incidence of adverse events. This can include regular short interval follow up with nurses to evaluate for adverse events and medication reconciliation with pharmacists to reduce the risk of hyper photosensitivity.

Case Presentation

C was a 36 year old Chinese male Fitzpatrick IV who presented to the clinic in early 2024 with concerns of mild bilateral cheek hyperpigmentation over the past few years.

He was otherwise healthy and denied any past medical or surgical history.

His mother had melasma and his father had solar lentigines.

He denied tobacco, alcohol, or drug use. He worked as a physician. He endorsed frequent outdoor activities but irregular sunscreen and facial product use.

Review of systems was unremarkable, specifically for endocrine dysfunction.

Examination demonstrated symmetrical mild macular brownish hyperpigmentation over the superior cheeks. This area was around 1 x 1 cm on both sides. In addition, there was significant rolling and boxcar scarring over the temples and cheeks. There was also a mild diffusely spread macular brownish hyperpigmentation across this area of the cheeks.

He further revealed that he had severe nodular cystic acne during puberty and had twice been on isotretinoin. He reported that he had since placed his acne troubles behind him and now only has the occasional solitary pustule.

There were no other hyperpigmented lesions identified on the neck or hands.

The macular brownish hyperpigmentation over the superior cheek were found under Woods lamp to have well circumscribed and accentuated borders suggestive of majority epidermal and trace dermal pigmentation and demonstrated prominent vascular network and a pseudoreticular network of multiple brown dots under dermoscopy.

The macular brownish hyperpigmentation over the acne scars demonstrated similar findings, particularly a pseudoreticular network with vascularity and telangiectasias.

C was diagnosed with mild melasma limited to the superior cheeks and acne scarring complicated by post inflammatory hyperpigmentation over the cheeks (70).

The validated modified Melasma Area Severity Index and Melasma Severity Scale was used to objectively determine the extent of facial hyperpigmentation related to melasma. His modified Melasma Area and Severity Index was 1.2. And his Melasma Severity Scale was mild.

He was counselled on both melasma, acne scarring, and post inflammatory hyperpigmentation. He was reminded of the importance of a daily face care routine, this included a broad-spectrum sunscreen, facial cleanser, and moisturizer. He requested a procedural intervention that would simplify and accelerate the process.

Chemical peel was the intervention of choice as it would not only reduce melasma but also improve the condition of his acne scars. In this case, a superficial chemical peel (GA 20%) was selected given his history of poor skincare and questionable compliance to reduce the risks of adverse effects. He was also started on adapalene 1% nightly with the aim of reducing melasma, improving acne scars, and as a primer for a chemical peel.

His first chemical peel was 1 month after initiation of adapalene nightly. Three coats of peels were applied for 3 minutes each. This was performed monthly for a total of 6 months.

His most recent follow-up was in early 2025 and there remained visible improvement in his overall skin quality and texture. There was also objective improvement in his mMASI at 0.6.

Discussion

Chemical peels have been a mainstay in the growing trend to age gracefully. Whereas skin laxity can be treated surgically with facial rejuvenation procedures such as a face lift these procedures are unable to improve skin texture and brightness. Although more commonly used to address fine lines, chemical peels can also be useful in the treatment of pigmentary irregularities and scarring. A PubMed database search with the key terms “melasma chemical peels” was used to identify research related to the use of chemical peels in melasma.

One of the first studies regarding the use of chemical peels in the treatment of melasma was performed in Singapore. Ten Chinese women Fitzpatrick IV and V with moderate to severe melasma were recruited. This nonblinded split face design had subjects apply GA 10% and hydroquinone 2% twice daily on the entire face and GA peels (20-70%) every 3 weeks to one half of the face for a total of 8 sessions. The peel was started at 20% and gradually increased at each subsequent session as tolerated. Contact time was also gradually increased until the 5min interval. Assessment was based on the Munsell colour chart and was performed by an independent dermatologist and the subject themselves. Although there was improvement in the peel group, the analysis found the difference to be statistically insignificant (71).

Although statistically insignificant, this early study was encouragement that chemical peels could play a role in the management of melasma. The study design could be strengthened by increasing sample size, randomization, double blinding, and use of a standardized strength/concentration of peel. Objective measures for melasma such as the colorimeter analysis, mMASI, and MELASQOL would also be an improvement compared to the subjective allocation of minor or major improvement. With respect to case study C, this study did not enlist any subjects of the male gender and given melasma’s relationship with hormonal changes during pregnancy and menopause, results from studies that include the male gender would serve as a stronger reference point.

There were numerous other similar studies based in India in the early 2000s that studied the use of GA in the treatment of melasma. Javaheri *et al* recruited 25 Indian women with MASI ≥ 15 for monthly GA peels 50% and found a reduction of MASI scores in 91% of patients (72). Sarkar *et al* studied 40 Indian patients with melasma with the GA peel group demonstrating better improvement compared to triple combination cream alone (73). Grover *et al* treated 15 Indian Fitzgerald III to V with fortnightly GA peels 10-30% and found good to fair response in melasma in >90% of patents (74). Khunger *et al* was most aggressive amongst these studies that were published within this short span of time. In his study 10 Indian patients were treated with weekly GA peel 70% vs tretinoin 1% in a split face design. MASI evaluation demonstrated significant decrease in melasma for both peels (75).

Even if there were similar deficiencies in these studies such as small sample size, lack of randomization and blinding, and insufficient objective measurements, these studies conclude that glycolic acid peels have demonstrable benefits in the treatment of melasma. Furthermore, this wealth of research on Indian females also alludes to the fact that melasma is more prevalent in females and darker skin tone communities.

GA peels have also been found to have demonstrable effect in recalcitrant melasma (failure to respond to 3 months or more of treatment). Erbil *et al* from Ankara, Turkey enrolled 28 subjects (27F 1M) with recalcitrant epidermal melasma in a prospective randomized controlled trial. Both groups received azelaic cream 20% bd and adapalene gel 0.1% qhs. The treatment group also received GA peels of gradually increasing strength starting from 20% for 3-5mins every other week for a total of eight sessions. There was a significant decrease in MASI in both groups at study completion (20 weeks) with better improvement in the GA group (83 vs 69%). The differences in scores were more pronounced late in the study when high concentration GA peels (≥50%) were in use. There were minimal adverse effects with three cases of mild post inflammatory hyperpigmentation that resolved by the end of the treatment period (76).

This study suggests that GA peels compound upon the benefits of topical treatment for even better outcomes. This is an important finding as patients are usually already on topical therapy prior to seeking additional adjuvant therapy. The fact that these outcomes were obtained in a population with recalcitrant melasma further supports the role of chemical peels as both the primary and secondary form of intervention especially in resistant cases.

The study can be strengthened with a larger sample size, split face design, and double blinding. MELASQOL can also be used to study quality of life outcomes. A longer study duration would also have been useful to counsel patients with regards to rate of recurrence, if any.

In addition to traditional GA peels, tretinoin mask peels have also been found to be beneficial in the treatment of melasma. Ghersetich *et al* enrolled 20 female subjects Fitzpatrick II to VI with bilateral epidermal melasma. They were treated with four sessions of tretinoin mask 10% for 1 hour every 3 weeks. There was a significant improvement in MASI and mexanmeter degree of pigmentation from baseline. There was no relapse in melasma noted at 1 year follow up. There was no difference in treatment response amongst darker skin types (Fitzpatrick V and VI). This distinction is relevant as darker skin tones have a tendency towards developing hyperpigmentation (77).

Although this study also suffers from small sample size, lack of double blinding, and lack of split face analysis, it does include a range of skin types and utilize objective measures such as MASI and mexanmeter analysis. In addition, this study stands out because of its long term follow up (1 year) compared to most of the available literature.

TCA peels are deeper peels that have also been studied in the treatment of melasma. Their depth of penetration should theoretically make them more effective in the treatment of dermal melasma.

Puri compared TCA peel 15% to glycolic acid peel 35% in 30 Indian patients with epidermal melasma. Peels were performed every 3 weeks for a maximum of six sessions or clearance of melasma. Subjective evaluation showed good responses in both GA and TCA groups (70% vs 64%). There was a significant decrease in MASI from baseline but no difference in MASI change between both groups. There were slightly more adverse effects in the TCA group namely burning (26.6% vs 6.6%), erythema (20% vs 10%) pain (6.6% vs 3.3%) cracking (6.6% vs 0%) and hyperpigmentation (13.4% vs 6.6%) (78).

The authors reported a conscientious decision to use a lower concentration of TCA to reduce the risk of hyperpigmentation, but outcomes suggested that hyperpigmentation, and other adverse effects were still much more common in the TCA group. Given that TCA generally functions as a deep peel, reducing its concentration and excluding patients with dermal melasma seemed to be counterintuitive to where it would be most efficacious.

Another comparison between GA 35% and TCA 20% was led by Brar in 2015. 50 Indian patients of recalcitrant epiderma melasma underwent three peels at three weekly intervals. Both groups demonstrated significant reduction in MASI (33.5% vs 34.8%) with no difference between groups. There were more adverse events in the TCA group with statistical significance in cracking (79).

More recently, Sahu *et al* compared GA 30%, LA 92%, and TCA 15% in the treatment of melasma. A sample size of 90 subjects was divided evenly into groups of 30. The peels were applied every 2 weeks for 12 weeks and MASI and QOL index were used for clinical evaluation. There was a significant decrease in MASI in the GA and TCA group but not the LA group. The improvement in QOL was higher in GA followed by TCA and LA. Adverse effects was noted mostly with TCA followed by GA and LA. These results were similar to the studies by Puri and Brar in that GA and TCA peels were equally efficacious with more adverse events in TCA peels (80).

These studies could be improved with documentation of Fitzpatrick type, randomized control, split face analysis, and additional objective measures such as the use of a colorimeter and MELASQOL.

In addition to stand alone TCA peel, Soliman *et al* studied the addition of ascorbic acid 5% (Vitamin C) in cases of epidermal melasma. 30 women Fitzpatrick III to IV with epidermal melasma were included in the study. Both groups received 20% TCA peel weekly for six sessions or until melasma was cleared with the treatment group receiving an additional 5% ascorbic acid cream daily. Both groups demonstrated improvement from baseline, but the ascorbic acid group showed significantly more reduction in MASI than control (44% vs 20%) at the end of the 16 week follow up period. This study lends further credence to the combinatory effects of chemical peels with topical creams (81).

The strongest study to date is a recent systematic review published by Sarkar *et al* in 2024. They identified a total of 24 studies, more than half of which were RCTs, with a total sample size of 1075. The total study duration ranged from 8 to 36 weeks with MASI used as one of many objective assessment tools. In this comprehensive and recent review of the literature, Glycolic Acid was found to be safest and most effective in the treatment of melasma (82).

Although this is the strongest paper available in the literature, a systematic review is only as strong as the studies it can include. Unfortunately, a meta-analysis could not be performed due to heterogeneity of data. Furthermore, there were only 8 studies that utilized a split face protocol. Regardless, the evidence strongly endorses the use of chemical peels, in particular GA, in the treatment of melasma.

Conclusion

Chemical peels are more commonly used as an anti-aging intervention but also have demonstrable effectiveness in the management of melasma. Interestingly, based on the literature available, its use appears to be most prevalent in India where the majority of patients are Fitzpatrick III and above and would theoretically be more susceptible to the adverse effects of hyper and hypopigmentation. These fears have thus far been unfounded as no study has reported an increase in hyper and hypopigmentation. However, it remains prudent to avoid medium to deep peeling in darker skin tones.

Mainstream media generally markets chemical peels in categories such as AHA, BHA, and TCA. However, their strength and depth of penetration can also be titrated based on the concentration of solvent, duration of application, and number of coats. Glycolic acid is the chemical peel most suitable for the treatment of melasma in terms of efficacy and adverse effects.

Although topical treatments such as hydroquinone, triple combination cream, and tretinoin remain the first line of treatment in melasma, chemical peels have proven to be an important adjunct with synergistic effect in the management of melasma. Priming with the above-mentioned products and proper skin care is necessary for optimal outcomes. In addition, the intervention itself only requires a short visit to the practitioner every few weeks and minimal downtime depending on the degree of exfoliation.

Patients on chemical peels should be frequently assessed with regards to increasing the peel concentration. In addition, laser mechanical exfoliation can be considered for dermal melasma and acne scarring.

CASE FOUR

LASERS

PICOSECOND ND:YAG, Q-SWITCHED ND:YAG, ABLATIVE AND NONABLATIVE FRACTIONAL

Introduction

Light Amplification by the Stimulated Emission of Radiation (Lasers) represent monochromatic (single wavelength), coherent (in phase), collimated (in parallel) high-intensity light that can be accurately focused into small spots of very high energy. The process involves the production of light within an optical cavity continuing a medium that may be gas, liquid, or solid. Lasers first gained popularity in the 21st century and advances in technology has revolutionised its use in the treatment of dermatological conditions since (83).

Lasers can be broadly categorised by their wavelength or pulse duration. Excitation of molecules of a specific medium releases a photon of light at a precise wavelength. Meanwhile, lasers in dermatology have evolved from continuous, quasi-continuous, pulsed (Q-switched nanosecond), and now to the latest generation of picosecond lasers.

Lasers have since emerged as a safe alternative option for treating melasma cases where the conventional methods involving topical creams and chemical peels have proven less effective (84).

This section will focus on the use of lasers in the treatment of melasma, and will discuss their mechanism of action, methods of administration, contraindications, and possible adverse effects and complications.

Mechanism of action

Lasers utilise a range of mechanism of action to address melasma based on their wavelength and pulse duration. The key elements in melasma include melanin, which has a broad absorption spectrum (630-1100nm), and melanosomes, which have a short thermal relaxation time (50-500ns) (85).

Fractional resurfacing lasers were introduced in 2004 and can be broadly categorised into ablative fractional lasers and non-ablative fractional lasers. Fractional lasers function via photothermolysis where laser energy is absorbed by water-containing tissues inducing selective thermal damage leading to the formation of microscopic thermal zones and the development of keratinocyte necrosis in the epidermis. This microscopic epidermal necrotic debris migrates towards the stratum corneum together with coagulated dermal components such as melanin (85).

Ablative Er:YAG is theoretically more efficient than CO2 due to better cutaneous absorption allowing for more superficial tissue ablation with less thermal damage. On the other hand, non-ablative fractional lasers leave the stratum corneum intact throughout the procedure. 1550nm non ablative fractionated laser is FDA approved for the treatment of melasma (85).

Nd:YAG lasers are increasing utilised in the treatment of melasma as the energy penetrates deeper into the dermis while causing minimal surrounding trauma. The newest generation picosecond lasers that utilise this medium can produce 1064nm wavelength laser with a much shorter pulse duration compared to Q-switched nanosecond lasers (85).

This superior pulse duration enables subthermolytic low fluence (laser fluence is a measure of the energy delivered per unit area – often expressed in joules per square centimetre (J/cm^2)) to disrupt pigment via a photoacoustic mechanism. This results in effective clearance of abnormal pigment while minimizing damage to keratinocytes and melanocytes (86). In addition, there also is subcellular selective photothermolysis demonstrated by a reduction in melanocyte dendrites in the epidermis and ultrastructural changes in melanosome at the microscopic level (87). Numerous brands such as PicoSure Pro, PicoPlus, and PicoWay have all been FDA approved for the treatment of melasma.

Methods of Administration

The patient is positioned supine, and the face is cleansed with non-inflammable products. There should be proper eye protection for patient and staff. Using the picosecond laser, settings of 1064nm 0.5J/cm^2 10Hz 8mm can be used to tone the entire face. The fluence can be titrated according to tolerance. The entire face should be treated three times in a single session for a total of around 2000-3000 shots. 755nm or 532nm at low fluence and spot size can be used to address epidermal lesions.

The patient is reminded of appropriate skin care such as moisturising and sunscreen before and after treatment to reduce the risk of complications.

Contraindications

There are relatively few contraindications for laser treatments, and most are relative rather than absolute. (88) Common sense dictates the avoidance of open wounds or active infections if the treatment is solely indicated for melasma. In addition, caution should be used in patients with darker skin tone (Fitzpatrick IV to VI) due to the elevated risk of dyspigmentation (86).

Adverse Effects

Traditional laser treatments based on selective photothermolysis results in destruction and death of pigment containing cells. This can lead to post inflammatory hyperpigmentation secondary to laser-induced basal layer damage and dermal inflammation (85).

Newer techniques based on the principle of subcellular selective photothermolysis uses high peak power and ultrashort pulse duration resulting in destruction of only melanin in the target cell. With low fluence, there is no cell death, and hence lower risk of inflammation and recurrence (85).

Regardless, laser treatments are considered a thermal burn, and it is not uncommon to have some degree of temporary pain, erythema, swelling, bleeding, bruising, blistering, and crusting. Long term adverse effects include infection, including the reactivation of herpes simplex, post inflammatory hyper and hypopigmentation, and scarring (83, 86).

A multidisciplinary interprofessional health care team approach should be utilized to ensure that patients achieve maximum benefit while reducing the incidence of adverse events. This can include regular short interval follow up with nurses to evaluate for adverse events and medication reconciliation with pharmacists to reduce the risk of hyper photosensitivity.

Case Presentation

D was a 55 year old Chinese female Fitzpatrick IV who presented in late 2023 with concerns of moderate bilateral cheek hyperpigmentation over the past couple decades.

She was otherwise healthy and denied any past medical or surgical history. She was a mother of two teenage children. She suspected her hyperpigmentation to have worsened post-menopause.

She denied any ongoing or recent medication use, specifically oral contraceptives or other hormonal products.

There was no family history of hyperpigmentation.

She denied tobacco, alcohol, and drugs. She endorsed regular sunscreen use and occasional trips to her aesthetician for facials.

Review of systems was unremarkable, specifically for endocrine dysfunction.

Examination demonstrated symmetrical moderate macular brownish hyperpigmentation over the cheeks. This area was around 4 x 4 cm on both sides. There was also trace macular brownish hyperpigmentation over the inferolateral forehead. This area was around 1 x 1 cm on both sides. There was no obvious hyperpigmentation over the neck or hands.

The macular brownish hyperpigmentation over the cheeks and inferolateral forehead were found under Woods lamp to have well circumscribed and accentuated borders suggestive of majority epidermal and trace dermal pigmentation and demonstrated prominent vascular network and a pseudoreticular network of multiple brown dots under dermoscopy.

D was diagnosed with moderate melasma.

The validated modified Melasma Area Severity Index and Melasma Severity Scale was used to objectively determine the extent of facial hyperpigmentation related to melasma. Her modified Melasma Area and Severity Index was 6. And her Melasma Severity Scale was moderate.

She was counselled on the prevention and treatment options for melasma and the importance of reapplying sunscreen during the middle of the day. She was concerned about her skin brightness and requested for procedural intervention with minimal downtime.

A picosecond laser was selected as this procedure has minimal downtime and has the additional benefit of improving skin tone. The initial settings were 1064nm 0.5J/cm² 10Hz 8mm 3 rounds around the face with a focus over the melasma lesions for a total of 2000-2500 shots per session. The fluence was then gradually uptitrated to 0.8J/cm² which produced a slight erythema upon treatment completion.

She has since undergone 12 sessions with visible improvement in melasma and skin tone. Her most recent follow-up was in April 2025 with visible improvement in skin melasma and skin tone. Her mMASI was 3.9. The importance of sun protection and possibility of lifelong treatment was reiterated.

Discussion

Laser treatments have been used in the treatment of melasma for many years and is gaining traction in recent years due to affordability and accessibility. In addition, developments in laser technologies have given rise to newer techniques and principles such as photoacoustic and subcellular selective photothermolysis. A PubMed database search with the key terms “melasma lasers” was used to identify research related to the use of lasers in melasma.

Now FDA approved for the treatment of melasma, the use of nonablative fractional 1550nm laser in the treatment of melasma was first studied in the early 2000s (89). Rokhsar *et al* enrolled 10 female subjects Fitzpatrick III to V with recalcitrant melasma to 4 to 6 treatments at 1 to 2-week intervals. They demonstrated significant improvement on both physician and self-evaluation (90).

Being one of the pioneering studies it has numerous flaws such as small sample size, lack of split face, double blind randomization, or any objective measures of melasma such as MASI or colorimeter analysis.

Another study based in Korea enrolled 25 subjects who underwent 4 monthly treatments. MASI decreased significantly at 4 weeks, but improvement waned by last follow up at 24 weeks. Hyperpigmentation was observed in 13% (91).

Nonablative fractional laser has also been compared against the gold standard triple combination cream. Kroon *et al* performed a randomised controlled investigator blinded study of 20 female subjects Fitzpatrick II to IV who underwent laser treatment every 2 weeks for a total of 4 treatments vs daily cream for 8 weeks (92). Although improvement was similar according to physician global assessment, subjects reported higher satisfaction in the laser group. Recurrence rate was 50% in both groups at 6 months. Wind *et al* utilised a similar study design with 29 subjects and further controlled with a split face approach but found that physician global assessment and patient satisfaction scores were significantly lower for the laser group (93). This could be attributed to a higher fluence used in the latter study 15mJ vs 10mJ.

The small sample size and lack of validated objective measures such as MASI, colorimeter index, and MELASQOL might have also led to discrepancies between outcomes. However, the contradictory findings in these two studies raise an even more important issue. It is perhaps just as critical, if not more so, to select the appropriate laser settings to achieve optimal results. Furthermore, these settings may vary depending on various patient factors such as Fitzpatrick skin type or MASI score and may even fluctuate based on the patient's skin condition on the day of treatment (recent sun exposure, degree of moisture).

The use of ablative fractional lasers has also been studied in the treatment of melasma. Angsuwarangsee in 2003 enrolled 6 female subjects with recalcitrant melasma to a split face study of alexandrite 755nm laser with or without ablative fractional CO2 laser. Three patients developed post inflammatory hyperpigmentation, and one patient developed hypopigmentation (94). Meanwhile Manoloto in 1999 treated 10 female subjects with recalcitrant melasma with ablative fractional Er:YAG and all developed post inflammatory hyperpigmentation (95).

These results suggest that ablative fractional lasers should be avoided due to the high rate of post inflammatory dyspigmentation. However, these early studies were of small sample size, lacked double blind randomisation, did not use objective measurements such as MASI or colorimeter analysis, and as earlier suggested, possibly suffered from the lack of modern-day machinery and practice recommendations.

A recent meta-analysis by Zhao *et al* in 2024 studied 14 randomised controlled trials which included 527 patients demonstrated noninferiority of ablative fractional lasers compared to other lasers in terms of MASI with only a few cases of reversible post inflammatory hyperpigmentation (96). This suggests that newer technology and updated practice parameters can improve clinical outcomes and reduce complications. This study also emphasised the importance of keeping up to date with the latest research especially high-powered studies with larger sample sizes and rigorous methodology such as double-blind randomisation and the use of objective measurements.

Q switched Nd:YAG lasers is the most widely studied laser in the treatment of melasma. Nearly 10 years ago, Sarkar *et al* published a review that included 10 studies and 446 patients of melasma. Of these 10 studies, 6 were randomised controlled trials. The consensus was that Q switched Nd:YAG had good results in melasma. However, the studies were generally of small sample size with an infrequent number of side effects in the form of dyspigmentation (85).

More recently there were two meta-analyses published by two different groups based in China. Lai *et al* from Beijing included 22 studies and 694 patients and concluded that standalone Q switched Nd:YAG reduced MASI significantly. Interestingly, they also found significant reduction in MASI score in ablative fractional laser but not non-ablative fractional laser (97). Meanwhile, Chen *et al* from Guangzhou included 12 studies and 358 patients that studied Q switched Nd:YAG alongside traditional topical therapy. There was no difference in MASI between Q switched vs topical therapy whereas combination therapy demonstrated a significantly greater MASI improvement. These findings suggest that Q switched Nd:YAG could be used as a standalone alternative for drug intolerance or used as an adjunct to further improve outcomes in patients already on topical therapy (98).

Picosecond laser has quickly grown from an emerging laser alternative in the treatment of melasma into a mainstay with multiple FDA approved machines. Its photoacoustic mechanism theoretically reduces downtime and adverse effects such as dyspigmentation.

In 2022, Hong *et al* enrolled 20 Korean patients with melasma and performed a randomised split face trial of either Picosecond Nd:YAG or Q switched Nd:YAG for 10 total sessions at 2-week intervals. Both groups demonstrated significant decreased mMASI scores with no statistical difference between two groups at any time point. There was also no difference in patient satisfaction and visual analogue scales between both modalities (99).

Feng *et al* replicated the study the following year with 18 patients. Findings were mostly similar, with significant MASI improvement compared to baseline and no difference in patient satisfaction. However, the visual analogue scale was significantly more painful in the Q switched group. The recurrence rate was 12.5% for both groups at 3-month post treatment (100).

Even though the sample size was small, these studies were of respectable strength due to its use of randomised split face study design and validated objective measurements such as the mMASI. An area of improvement would have been to use the MELASQOL rather than a patient satisfaction scale due to it being a recognized disease specific psychometric instrument.

The picosecond alexandrite 755nm has also been found to be useful in the treatment of melasma. 37 patients were enrolled in a multicentre randomised double blinded split face study to either receive monthly laser monotherapy or laser and topical tranexamic acid for a total of three sessions. Both groups demonstrated significant improvement compared to baseline in MASI and skin texture at 6months post final treatment. Laser and topical tranexamic acid had significantly more redness and sensitivity during the immediate post procedure duration but was also superior to laser monotherapy in terms of MASI improvement (101).

China with its recent industrial and technological revolution is unsurprisingly the leader of high-powered research of lasers in the treatment of melasma given that its monoethnic population of Fitzpatrick III to IV skin types is particularly vulnerable to melasma. Also based out of China, Feng *et al* included 6 randomised controlled trials that compared picosecond laser with conventional treatments. They found that picosecond 1064nm laser significantly reduced MASI/mMASI without significant side effects. On the other hand, picosecond 755nm laser did not significantly improve melasma (102). Another meta-analysis including 20 studies and 1182 patients also suggested that picosecond 1064nm laser reduced MASI significantly (103).

This meta-analysis lacked sufficient data to perform a subgroup analysis on the efficacy of picosecond 595nm and 532nm lasers. Furthermore, this meta-analysis did not consider the psychosocial component which is just as important as the MASI in the treatment of melasma. This can be objectively studied with MELASQOL.

Another recent meta-analysis included 9 randomised controlled studies with 364 patients studied the use of laser, drug, and combination therapy and found no difference in MASI/mMASI between these groups (104).

A meta-analysis is the strongest evidence available in literature, but they are only as strong as the studies included. Although most of the studies included in these meta-analyses were randomised controlled trials, there appears to be significant heterogeneity in methodology which affected the analysis. This can only be resolved with higher quality primary studies utilising randomised controlled split face designs with large sample size, long follow-up duration, and objective measurements. It would be even better if there was a degree of deliberateness regarding the inclusion criteria such as controlling for Fitzpatrick type, epidermal/dermal melasma, and newly diagnosed or recalcitrant melasma.

Regardless, there is already more than sufficient data to suggest that newer lasers with updated practice principles have a significant role to play in the treatment in melasma, whether standalone or in combination with other treatment modalities.

Conclusion

Lasers are a rapidly developing tool in the management of melasma. The past two decades have seen a significant leap in technology with the development of more responsive machines. Meanwhile, practitioner technique has also evolved based on updated laser principles such as subthermolytic low fluence and photoacoustics. These advances have combined for superior outcomes in the treatment of melasma. Furthermore, the tech boom has led to greater affordability and accessibility, allowing lasers to become a reasonable alternative for the masses.

Lasers are generally associated with risks related to dyspigmentation especially in darker Fitzpatrick skin types. However recent studies, in part due to improved technology and guidelines, suggest these concerns might be overblown. As an aside, a significant number of recent studies have been published out of eastern Asia which is also most representative of case study D. Care should be taken in the extrapolation of study results onto other Fitzpatrick skin types as lighter skin tones might be more susceptible to superficial burns and longer downtime, whereas darker skin tones might have an increased risk of hyper and hypopigmentation.

Picosecond Nd:YAG is a figurative “golden child” with multiple machines obtaining FDA approvals for the treatment of melasma. It is believed the use of subthermolytic low fluence and photoacoustics minimizes downtime and thermal injury, thus reducing the risk of post inflammatory hyperpigmentation and scarring. Popular alternatives include nonablative fractional laser and Q switched Nd:YAG.

Topical combination therapy remains the first line management of melasma but with the rapidly evolving landscape, it is a strong possibility that the use of both triple combination cream and picosecond laser could become the first line management of melasma in the not-so-distant future.

CASE FIVE

INTRADERMAL TRANSAMIN

Introduction

Over the past decade, the aesthetics market has burgeoned in response to an increasing acceptance towards the use of injectable therapies in society. As such, it is no surprise that there is also an expanding volume of literature regarding the use of injectables in the treatment of melasma.

One of the most widely studied injectable drugs in the treatment of melasma is Trans-4-(Aminomethyl)cyclohexane carboxylic acid, otherwise known as Tranexamic Acid or Transamin. The treatment is commonly administered via microinjections that penetrate the skin to deliver droplets of medication in a controlled fashion directed to the intradermal layer of the lesion (105).

Despite the seemingly invasive nature of the procedure relative to other melasma treatment alternatives, there is a wealth of literature describing intradermal injections of transamin as safe and efficacious with minimal side effects. In current practice, transamin is usually considered an adjunctive therapy or as a complement to those who are already undergoing routine aesthetic treatments.

This section will focus on the use of intradermal transamin in the treatment of melasma, and will discuss their mechanism of action, methods of administration, contraindications, and possible adverse effects and complications.

Mechanism of action

Transamin was serendipitously discovered to have a beneficial effect in the treatment of melasma by Nijo Sakado in 1979 when it was identified to be the cause of significant improvement in hyperpigmentation during the treatment of a patient with chronic urticaria (106).

Transamin is most well-known for its use as an antifibrinolytic in menorrhagia but has more than one principle behind its activity in the treatment of melasma. Namely, it has anti-melanogenic, anti-angiogenic, and anti-inflammatory influences that work in tandem, directly and indirectly, to reduce melasma (107).

The direct anti-melanogenic effect of Transamin is regulated by numerous mechanisms (107).

1) Transamin blocks the lysine-binding site of plasminogen and inhibit the synthesis of arachidonic acid. This reduces melasma as arachidonic acid and its metabolite prostagladin are both involved in the synthesis of melanin and the production of melanocyte stimulating hormone.

2) Transamin also reduces the activity of plasmin which results in inhibition of interaction between melanocytes and keratinocytes which leads to reduced UV induced tyrosinase activity in melanocytes and a subsequent decrease in melanin production.
3) Transamin is structurally similar to tyrosinase and is postulated to act as a competitive inhibitor which would further decrease melanin synthesis.
4) Transamin inhibits the activation of VEGF receptors in normal melanocytes thereby reducing tyrosinase activity.
5) Transamin prevents the activation of melanocytes and injured keratinocytes by inhibiting the plasminogen activator system. This leads to long term inhibition of melanocyte activation and reduces the recurrence rate.
6) Transamin can suppress melanin synthesis by inhibiting the release of paracrine melanogenic factors which usually stimulate melanocytes.
7) Transamin can promote the degradation of related transcription factors thus decreasing tyrosinase and therefore melanin synthesis.

Its anti-angiogenic effect reduces the vascular network that supplies the production of melanin. This is believed to be due to the inhibition of capillary proliferation via the reduction of the number and activity of mast cells and also inhibition of the plasminogen/plasmin system which leads to reduced fibroblast growth factors and subsequent reduced number of blood vessels, near total disappearance of mast cell activation and elimination of reperfusion damage (107).

Lastly its anti-inflammatory effect reduces free arachidonic acid and inhibition of prostaglandin E2 decreasing melanocyte activation and melanin production (107).

Methods of Administration

Transamin can be administered either topically, per oral, or via injection in the treatment of melasma. Compared to topical and oral administration, intradermal injections bypass the skin barrier and penetrate the appropriate layers with controlled precision while reducing the risk of systemic effects.

Microinjections are a minimally invasive procedure that involves direct percutaneous injection targeted at the intradermal layer to address the melanocytes. This is performed with a short and small gauge (34G 4mm) needle to inject a trace amount (0.05-0.1ml) of transamin. Injections are spaced 1cm apart. The dosage can be titrated according to clinical condition and practitioner experience with current literature recommendations ranging from 4mg/ml to 100mg/ml. A bleb should be visible upon completion. Treatment frequency and duration vary and can range between weekly to monthly for a minimum of 4 sessions (105).

This is not to be confused with microneedling which is another minimally invasive method usually performed with a 1.5mm needle at around 0.1-1.5mm penetration depths based on the anatomic location and pressure/suction applied prior to application of topical transamin (105).

Microinjection is time consuming and requires for a skilled practitioner but allows for greater control of drug delivery. On the other hand, microneedling requires special tools and associated costs but will ensure even distribution of product into the skin (105).

In addition to facilitating drug delivery across the stratum corneum, the process of microneedling, and to a certain degree microinjection, is also believed to stimulate the wound healing response and activate neocollagenesis and neoelastogenesis leading to reduced scarring and wrinkling (105).

The area of interest should be sterilized before and after the procedure. Topical anaesthetic is frequently applied pre-procedure to improve the experience.

Contraindications

There are few contraindications for intradermal transamin such as open wounds and active infections.

Intradermal transamin is safe given its low absolute dose and even lower systemic distribution. Even at the highest concentration documented in literature for the treatment of melasma (100mg/ml), the total dose delivered will still be much smaller than the minimum treatment dosage of 1000mg three times a day for haemostasis and is thus unlikely to cause significant haemostatic side effects (107).

However, it is still important to be attentive towards medical and surgical conditions that might be adversely affected by the introduction of an antifibrinolytic. A detailed history should be obtained prior to the procedure especially to evaluate risk factors such as clotting disorders (DVT, PE, thrombophilia), drug drug interactions (aspirin, plavix, warfarin), immobility, hormone therapy, bleeding, cancer, and recent surgery.

Adverse Effects

The adverse effects of transamin injection include pain, burning, bleeding, erythema, swelling, and ecchymosis. These side effects are generally mild, tolerable, and transient and disappear after a few days. Local anaesthetics can be used to reduce pain. Ice packs can also reduce pain, swelling, and bruising. Occasional reports of hypopigmentation, acne formation, post inflammatory hyperpigmentation, and infection have also been reported (107).

Systemic side effects are rare in intradermal injection. For completeness, the most common systemic side effects include gastrointestinal discomfort and decreased menstruation. Gastrointestinal discomfort can be reduced by administration of the drug after meals. Other side effects include headache, transient amnesia, blurred vision, vertigo, tinnitus, facial pruritus and numbness, periorbital and lip swelling, facial hypertrichosis, palpitations, lethargy, myalgia, joint pain, tremors, and dysmenorrhea (107). Within the melasma community, it is perhaps prudent to obtain a detailed menstrual history prior to initiation of the drug.

A multidisciplinary interprofessional health care team approach should be utilized to ensure that patients achieve maximum benefit while reducing the incidence of adverse events. This can include regular short interval follow up with nurses to evaluate for adverse events.

Case Presentation

E was a 50 year old Chinese female Fitzpatrick III well-established patient at the clinic who attended for regular upper face (frontalis, procereus, orbicularis oculi) botox who was concerned about moderate bilateral cheek hyperpigmentation that had gradually worsened since 2023.

She was otherwise healthy and denied any past medical or surgical history. She was a mother of two teenage children. She had suspected her hyperpigmentation to have worsened significantly during menopause.

She denied any ongoing or recent medication use, specifically oral contraceptives, other hormonal products, or haemostatics/antifibrinolytics.

There was no family history of hyperpigmentation.

She denied tobacco, alcohol, and drugs. She endorsed twice daily sunscreen use, nightly adapalene use, and regular facials at her aesthetician.

Review of systems was unremarkable, specifically for endocrine and haematological dysfunction.

Examination demonstrated symmetrical moderate macular brownish hyperpigmentation over the cheeks. This area was around 2 x 1 cm on both sides. There was no obvious hyperpigmentation over the neck or hands.

The macular brownish hyperpigmentation over the cheeks was found under Woods lamp to have well circumscribed and accentuated borders suggestive of majority epidermal and trace dermal pigmentation and demonstrated prominent vascular network and a pseudoreticular network of multiple brown dots under dermoscopy.

E was diagnosed with mild melasma.

The validated modified Melasma Area Severity Index and Melasma Severity Scale was used to objectively determine the extent of facial hyperpigmentation related to melasma. Her modified Melasma Area and Severity Index was 1.8. And her Melasma Severity Scale was mild. The validated MELASQOL was used to determine the subjective impact on her quality of life (108). Her MELASQOL score was 54.

She was counselled on the prevention and treatment options for melasma and elected for a trial of intradermal transamin. She indicated her experience and tolerability to injections. Also, she decided against triple combination cream given her already lengthy daily skincare routine. She also had concerns about the limited duration of therapy, possibility of recurrence, and risks of exogenous ochronosis.

She was treated with monthly intradermal transamin via microinjection at 50mg/ml for a total of 1ml localized to the hyperpigmented areas.

She has since undergone 12 sessions. Her most recent follow-up was in April 2025 with mild improvement in skin melasma. Her mMASI and MELASQOL had improved to 1.2 and 24 respectively.

At her most recent follow up, treatment cessation and risk of recurrence was discussed. She elected to continue with monthly treatments and inquired about adjunctive interventions. She was offered combination intervention with picosecond laser to achieve a synergistic effect for a stronger and longer lasting clinical outcome.

Discussion

Transamin was first discovered serendipitously to have a skin lightening effect in 1979. Its use in the treatment of melasma has since been refined in combination with a growing acceptance towards minimally invasive aesthetic procedures. It is now often administered via microinjection to the intradermal layer which allows direct penetration of the drug to the lesion of choice while avoiding systemic side effects. A PubMed database search with the key terms “melasma transamin/tranexamic acid intradermal” was used to identify research related to the use of intradermal transamin in melasma.

One of the earliest studies assessing the efficacy and safety of intradermal melasma was from South Korea in 2006. The authors recruited 100 women who were treated with 0.05ml 4mg/ml transamin at 1cm intervals weekly for 12 weeks. A significant decrease in MASI was observed after 8 weeks with further improvement at study completion. Patient self-assessment was predominantly fair. There were minimal side effects (109).

This was not the strongest study design but demonstrated that intradermal transamin was a safe alternative to traditional modalities of melasma treatment and paved the groundwork for more robust studies to come over the next couple decades.

Two separate groups from Pakistan studied the efficacy of transamin in the treatment of melasma in quick succession. Kaleem *et al* recruited 60 subjects for a split face study of either 4mg/ml transamin or normal saline every 2 weeks for 12 weeks and found significant decline in MASI score in the transamin group (110). Meanwhile, Mehmood *et al* recruited 11 outpatients who were treated with 4mg/ml transamin weekly for 6 weeks and found significant improvement in mMASI score with minimal side effects (111).

Badran *et al* from Egypt studied the effect of different concentrations of intradermal transamin in the treatment of melasma. 60 female subjects were randomized into 3 groups of either intradermal transamin 4mg/ml or 10mg/ml every 2 weeks, or 10% topical transamin twice daily for a total of 12 weeks. MASI reduction was significantly greater in the 10mg/ml group, followed by 4mg/ml. This suggests a 10mg/ml concentration is superior to 4mg/ml in the treatment of melasma (112).

A small study from Thailand included 5 Fitzpatrick type IV and V subjects on 4mg/ml transamin every 2 weeks for 7 sessions. There was significant improvement of mMASI at 16 weeks. However, this improvement was no longer significant at 48 weeks although severity remained improved from baseline. This suggests transamin might require several treatments before benefits are clinically clear and might require long-term maintenance therapy (113).

This study is particularly interesting because of its long follow-up duration compared to most other existing studies. Unfortunately, it has too small a sample size to draw any significant conclusions from.

In addition to the above studies, numerous researchers have also attempted to contrast transamin with traditional treatments to study its relative safety and efficacy.

In 2019, Pazyar *et al* included 49 subjects in a split face trial to receive either 4mg/ml or 10mg/ml intradermal transamin every 2 weeks for 12 weeks vs 4% hydroquinone. All groups demonstrated a significant decrease in MASI score at treatment end (24 weeks). However, 4mg/ml resulted in significantly less improvement compared to the other 2 groups. This further reiterated that 10mg/ml transamin was likely a more effective dose (114).

This study utilised split face design and objective measurements such as the MASI. However, subjective measures of patient satisfaction such as MELASQOL should also be included in the outcomes.

The next year, 60 Chinese subjects were randomised to receive either 5% intradermal transamin, 2% hydroquinone, or 1.8% liposomal transamin twice daily. All groups reported “more than 50% improvement” with effect best in the intradermal transamin and hydroquinone group. The erythema index was reduced in both transamin groups. Dermatoscopy found reduced brown granules in all groups, and reduced telangiectasia in transamin groups (115).

This study could have been stronger with the use of double-blind split face design, objective measurements such as mMASI, and subjective measurements such as MELASQOL. The study stands out because it includes post-treatment dermatoscope findings which supports the antimelanogenic and antiangiogenic properties of transamin.

In the same year, Meymandi *et al* from Iran entered 70 subjects into a single blind randomised trial of either 4% intradermal transamin monthly or 4% hydroquinone nightly. There was significant improvement in melasma for both groups at the end of the treatment (12 weeks). There was no statistical difference between both groups in terms of MASI score and physician and patient assessment (116).

This study was slightly more robust with its use of MASI as an objective measurement. However, it could be improved with the use of double-blind split face design and subjective measurements such as MELASQOL. Furthermore, comparisons of pain and procedure tolerability would also be interesting as one modality requires a greater degree of invasiveness.

2 years later, Mushtaq *et al* from Pakistan performed a similar study with a much larger study size. They recruited 290 subjects with melasma duration greater than 6 months with no treatment in the past 3 months and a MASI score greater than 10 were randomized to receive either 0.5ml 50mg/ml intradermal transamin weekly or 4% hydroquinone for 12 weeks. Results found transamin to be significantly more efficacious than hydroquinone (117).

This study had great potential given its large sample size but unfortunately the lack of clear concise objective measures reduces the utility of the study. According to the authors, efficacy was evaluated based on the fall in MASI score from baseline, but there was no clear indication on how this was defined. Presumably, any decrease in MASI score would be considered an efficacious outcome but this might not be statistically or clinically significant.

Pazyar *et al* performed a randomized double blinded trial with 48 subjects treated either with 100mg/ml intradermal transamin or 4% hydroquinone. Both groups demonstrated a significant decrease in MASI after 3 months with no difference between both groups. All transamin subjects reported mild burning pain without serious adverse effects. 100mg/ml is one of the highest concentrations studied in literature and does not yet appear to have superior outcomes compared to 50mg/ml. Regardless, the studies thus far agree that intradermal transamin is at the very minimum non-inferior to topical hydroquinone in the treatment of melasma (118).

This study was more robust than the previous studies as it was a double-blind study that directly compared MASI scores. The authors also attempted to discuss pain tolerability although validated measurements such as the VAS would have strengthened the paper whereas measurements of wellbeing could be studied with MELASQOL. Future studies should include multiple centres and larger sample sizes.

Transamin and hydroquinone have also shown to have superior outcomes when used in combination. Techranchinia *et al* enrolled 55 subjects to assessor and analyst blinded randomised split face trial to either 100mg/ml transamin every 4 weeks for 4 sessions and 4% hydroquinone or 4% hydroquinone alone. Both groups demonstrated significant reduction in MASI scores with outcomes significantly better in the combination group at 16 weeks. Patient satisfaction was also higher in the combination group (119).

This study included a respectable sample size, blinded both assessor and analyst, and utilised validated objective measurements. It would have been even better had MELASQOL, a validated disease specific subjective measurement, been used rather than a four-grade patient satisfaction questionnaire.

In addition to comparisons with traditional topical treatments, intradermal transamin has also been compared and/or combined with newer treatments such as laser therapy. Otb *et al* from Egypt published a small study comparing intradermal transamin with Er:YAG laser in the treatment of melasma. A split face study of 28 subjects found that MASI was significantly decreased on the transamin side and was associated with lower costs (120).

Hawwam *et al* also from Egypt enrolled 40 female subjects in a split face 12-week study to either intradermal transamin or intradermal transamin and Q switched Nd:YAG. There was a statistically significant decrease in mMASI score in combination treatment compared to monotherapy at both 12 weeks and 24 weeks follow-up suggesting that combination transamin and laser treatment is safe and more efficacious than monotherapy (121).

These studies included split face study between transamin and lasers but would be more robust if the study design was randomised double-blinded with a larger sample size. MELASQOL could also have been included for a validated assessment of patient satisfaction.

Poostiyan *et al* studied the difference between microinjections and microneedling in a robust randomized assessor blind split face trial with 27 female subjects who were treated with 100mg/ml transamin every 4 weeks for a total of 3 sessions. There was a significant improvement in mMASI from baseline with no intergroup difference. VAS found less pain in the microneedling group. However, side effects including erythema, scaling, and oedema were also significantly higher. There was one reported case of post inflammatory hyperpigmentation in the microneedling group (122).

In addition to transamin, ascorbic acid is another commonly used agent for skin lightening.

Pazyar *et al* first compared 500mg/5ml transamin with 500mg/ml ascorbic acid every 2 weeks for 3 sessions and found significant improvements in both groups. Although there was a stronger response in the transamin group, the difference was not significant (123). Thereafter, he enrolled 24 subjects to a double-blind randomised split face study to either 50mg/ml transamin and 50mg/ml ascorbic acid, or 50mg/ml transamin every 2 weeks for 12 weeks. Both groups had significantly decreased MASI scores compared to baseline with the combination group significantly superior at 8 and 12 weeks. Burning sensation was also significantly more prominent in the combination group (124).

These are two studies with strong study design that could be further improved by involving multiple institutions and recruiting a larger sample size. Patient satisfaction can also be evaluated with the MELASQOL. In addition, follow-up could be extended to evaluate for recurrence.

The majority of intradermal transamin studies for the treatment of melasma have been performed within the past 5 years and the clinical community would benefit from a large multicentre randomised double blinded split face study of various concentrations and doses of transamin in the treatment of melasma. Subgroup analysis for different Fitzpatrick skin types, epidermal vs dermal melasma, untreated vs recalcitrant condition would also be possible with a larger sample size. In addition to objective measurements such as MASI, validated disease specific subjective measurements such as MELASQOL should always be included in the treatment of a primarily aesthetic condition such as melasma. Furthermore, longer follow-up duration could be implemented to study recurrence rate. Lastly, combination therapies with topical, laser, and other injectables should also be reviewed.

Conclusion

Transamin is an antifibrinolytic that was serendipitously discovered to modulate hyperpigmentation in the 1970s. It has since been used in the treatment of melasma in various formulations. The growing acceptance towards minimally invasive aesthetic procedures has led to a rising popularity in the use of transamin via intradermal microinjections.

In the hands of a skilled practitioner, it is a quick and safe procedure with minimal downtime. In addition, any side effects are often mild and transient (105). In comparison, gold standard triple combination creams do carry the rare, but significant, long-term complication of exogenous ochronosis.

Literature has not only demonstrated its efficacy in combination with other modalities to improve outcomes in the treatment of melasma but also alluded that it is viable as a monotherapy alternative. However, more robust randomised controlled trials are needed to elucidate the optimal dose, concentration, frequency and duration of treatment. Currently, a concentration of 10-100mg/ml, 0.05-0.1ml per injection, at 1cm intervals, with weekly to monthly frequency, for at least 4 sessions would be a reasonable treatment protocol with the caveat of uncertain recurrence rate upon treatment cessation. Patients already on transamin can consider admixing ascorbic acid into the solution for injection.

Intradermal transamin efficacy and minimal transient side effects might just become part of a melasma treatment triad together with topical triple combination cream and picosecond Nd:YAG laser.

DISCUSSION

RECOMMENDATIONS

CONCLUSION

Discussion

Melasma is a worldwide condition that has a preponderance to afflict younger women of darker skin tones. It presents most commonly as symmetrical hyperpigmented macules across the upper cheeks. Its multifactorial pathophysiology where overproduction of melanin is trapped within the skin is believed to be due to a combination of genetic predisposition and environmental exposure.

Overlooked Undertreated

It remains a dermatological condition that is commonly overlooked and undertreated because of its lack of association with significant physiological complications such as malignant transformation. Unfortunately, this focus on physical health results in a failure to recognize the negative psychosocial effects upon an already vulnerable populace. This is subsequently further amplified given the condition's chronological relationship with pregnancy and childbirth which is already associated with significant physical and emotional stress.

Quality of Life

Fortunately, a societal shift towards embracing quality over quantity of life has led to the increased awareness towards melasma over the past couple decades. During this period, a growing number of studies have demonstrated a strong negative correlation between melasma and quality of life. Investigators across the world, from San Francisco, Greece, South Africa, Iran, and Nepal have simultaneously begun to recognize and address the needs of the younger generations who now place greater emphasis on looking and feeling good (125-129). This has in turn stimulated the development of more effective and affordable interventions for the treatment of melasma.

The treatment of melasma begins with a thorough evaluation to rule out any suspicious lesions that might prompt further investigation. The common inciting factors such as sun exposure, oral contraceptive use, and pregnancy should be discussed. The pattern of distribution should be noted as it can be suggestive of the presence of inciting factors. Woods Lamp and Dermoscopy are accessory examinations that can distinguish between epidermal, basal, and mixed melasma. Validated standardised measurement scales such as the mMASI and MELASQoL should be tracked across clinic visits. In particular, the use of MELASQOL cannot be underestimated given the primary goal of melasma treatment is to improve quality of life via the reduction of hyperpigmentation.

The MELASQoL was developed by Balkrishnan *et al* in 2003 to address this very conundrum (130). This scale consists of only 10 questions scored from 1(not bothered at all) to 7 (bothered all the time); the higher the score the lower the quality of life. The domains it studies includes work, family, social life, sexual relationships, recreational leisure, physical health, financial matters, and emotional wellbeing. These domains have proven to have high correlations with other validated tools that have withstood the test of time such as the DLQI. It also has a high internal consistency rate. In fact, its emphasis on emotional and psychological aspect has demonstrated in some instances to be superior to other dermatological quality of life indicators (131, 132).

Zhu *et al* performed a meta-analysis of 1398 patients across 14 studies (six in Asia, four in South America, three in Europe, and one in Oceania). They concluded that melasma affects numerous aspects of life, with the greatest influence on leisure, emotional health, and social lives with feelings of confusion, frustration, embarrassment, and loss of confidence, making patients feel unattractive and affecting their relationships. However, the physiological severity of melasma was not a comprehensive indicator of quality of life (133).

Most of the studied population in this meta-analysis were female. This may be representative of the disease demographic, but care should be exercised when extrapolating results onto a male patient. In addition, the geographical reach of the compiled studies is representative of the global prevalence of the condition. Curiously, the authors did not identify any North American literature for inclusion. This could have been due to an incomplete literature review, sociocultural differences in disease perception across continents, and even racial or healthcare system biases.

Insurance Exclusion

In fact, Sun *et al* based in the US wrote about barriers to treatment secondary to insurance coverage gap for conditions typically seen in patients of colour. Comparing rosacea (often diagnosed in Fitzpatrick I and II) to melasma (Fitzpatrick III to V), they found that 32% of patients with rosacea obtained a prescription compared to 1.84% of patients with melasma, an odds ratio of 27. This suggested that many first line treatments for melasma may be less frequently covered by insurance than those for rosacea, preventing darker skinned patients from assessing appropriate healthcare (134).

Unfortunately, the lack of insurance coverage in turn tends to lead to reduced funding opportunities for research, fewer clinical trials, and poorer patient care. This is reflected in the number of publications per research funding related to melasma published in the US (579) compared to other countries with public healthcare such as England (146), Italy (131), and Germany (128). The increased attention placed upon the condition can also be observed in Asian countries such as China (471), South Korea (213), and India (161) (135).

Emerging Theme of Multimodality Treatment

Melasma is a dermatological condition that results in a change in the physiological appearance that primarily afflicts the psyche (136). The treatment of melasma is lengthy and requires patience, compliance, and delayed gratification. To achieve this, it is imperative that providers are comfortable with all available interventions to formulate a treatment plan that integrates seamlessly into the patient's lifestyle.

In addition, with the growing number of interventions available to providers, the ideal management for melasma should be a multimodality patient-directed treatment that facilitates clinical improvement and psychosocial wellbeing.

Case Reflections

To illustrate this, five patients with distinct medical and social histories presenting with different phenotypes of melasma were carefully selected to highlight an optimal management plan for each scenario.

Prior to the initiation of medical intervention, all patients were reminded that the consistent use of sunscreen SPF 50 and ++++ will be integral to clinical improvement.

Case 1 was a young mother of three kids who presented with mild epidermal melasma. In this case, the use of topical hydroquinone, with a view of transitioning to triple combination cream, was the ideal intervention for mild and epidermal melasma combined with a busy schedule caring for her kids. The patient experience was positive, and the clinical outcome was good.

Hydroquinone 4% remains the most extensively studied in the treatment of melasma. It remains a mainstay due to its accessibility, affordability, and ease of application. Despite its side effect profile, a significant majority of studies have demonstrated the risk of exogenous ochronosis to be negligible. Meanwhile, TCC is the most effective treatment with safety established for up to 12 months of use and should continue to be a first line intervention in the treatment of melasma.

Case 2 was an older woman who worked as a nail aesthetician with long term exposure to indoor UV radiation who presented with moderate-severe epidermal melasma. In this case, the use of topical adapalene was the ideal intervention for moderate-severe epidermal melasma with a history of exogenous ochronosis secondary to use of an unknown skin lightening medication. This was a lower risk product compared to triple combination cream and produced a satisfactory outcome. The patient experience was positive especially after transition to adapalene to reduce retinoid-associated erythema.

Retinoids such as Tretinoin and Adapalene have also been used in the treatment of melasma with much success. The newer generations of retinoids such as Adapalene have selective activity on RAR-β which reduces its major side effect of erythema and burning and improves its overall tolerance. Compared to HQ/TCC there are also no reported cases of exogenous ochronosis. However, consistent long-term use of at least 6 months is necessary for clinical improvement.

Case 3 was a young male physician with poor skin care habits, infrequent sunscreen use, and significant acne scarring from childhood who presented with mild epidermal melasma. In this case, monthly glycolic acid peels were the ideal intervention because it would not only simultaneously improve both melasma and acne scars, but it was also an intervention that was less reliant on patient compliance compared to nightly topical creams. The patient experience was positive, and the clinical outcome was good.

Chemical peels are a relatively inexpensive option that can performed at monthly intervals. Glycolic acid peels have been found to have the best efficacy and safety profile in the management of melasma. Despite the obvious risk of erythema, burning, and PIH, many studies published out of India where the populace is generally Fitzpatrick IV and darker suggest that these concerns may be exaggerated. Further studies should compare the large variety and concentration of peels that are available in the current market to create guidelines that maximize efficacy while minimizing adverse events.

Case 4 was an older woman who presented with moderate mixed epidermal and basal melasma with secondary concerns about her skin tone. In this case, the ideal treatment was low fluence picosecond Nd:Yag to optimize penetration of basal melasma while also providing a simultaneous benefit towards overall skin tone. The patient experience was positive, and the clinical outcome was good.

Picosecond Nd:Yag have exploded in popularity and is the subject of much ongoing research in the treatment of melasma. There have even been research suggesting that lasers are more effective than traditional topical products. The use of subthermolytic low fluence and photoacoustics minimizes downtime and thermal injury, thus reducing the concern for post inflammatory hyperpigmentation and scarring. Picosecond Nd:Yag should be considered as first line management in the treatment of melasma.

Case 5 was an older woman who presented with mild mixed epidermal and basal melasma. She had an impressive skincare routine and extensive injectable experience. In this case, the ideal treatment was intradermal transamin injection given her ready attitude towards injectables and desire to avoid hyperpigmentation risks such as post inflammatory hyperpigmentation and exogenous ochronosis. The patient experience was positive, and the clinical outcome was good.

Transamin has well-studied anti-melanogenic, anti-angiogenic, and anti-inflammatory properties whereas microneedling facilitates accurate drug delivery to the appropriate depth while bypassing the systemic organs, ensuring clinical benefit while minimizing systemic side effects. This lesser-known intervention enables effective drug delivery in lieu of laser therapy or chemical peels which can induce post inflammatory hyperpigmentation.

Limitations

Melasma remains an understudied disease despite its global prevalence. The common limitations to most of the current studies are related to study design, sample size, and outcome measurement. Understandably, it must not be easy to obtain funding to treat a condition disproportionately overlooked by both clinicians and insurance providers.

Future studies should adhere to the use of a randomised, double-blind, split-face design with a long follow up duration. All subjects should be required to adhere to twice daily SPF 50 ++++ sunscreen use prior to enrolment. Researchers should recruit a large sample size of subjects and at minimum, control for Fitzpatrick skin type, gender, age, history of pregnancy, history of melasma (newly diagnosed or recalcitrant), and type of melasma (epidermal, basal, mixed) with subsequent subgroup analysis. Interventions should have a clearly defined and replicable dose, concentration, and frequency. Outcomes should prioritize the use of both validated scales; the objective mMASI and subjective MELASQoL. Additional metrics can include reflectance spectrophotometer, colorimeter, and skin biopsies.

Recommendations

Melasma is an acquired chronic physiological condition associated with proven psychosocial repercussions. Optimal management of the condition is complex and requires a robust understanding of both the patient and their condition.

It is recommended to ensure all patients are on twice daily sunscreen SPF 50 ++++ prior to initiation of any treatment. Photos should be taken before and after every follow-up.

The table below summarizes some of the most popular interventions available in current literature including their advantages and disadvantages. It is important to remember that each case should be considered independently as no two patients are similar. Unlike other medical conditions, there are numerous efficacious options in the treatment of melasma and the cornerstone to successful management of melasma is compliance. To achieve this, it is critical that primary care practitioners ensure that the treatment plan considers key factors such as affordability, downtime, and pain tolerance.

Treatment	Modality	Dosing Frequency	Cost	Optimal Melasma Depth	Downtime	Pain	Erythema	PIH	Extreme Adverse Effects
HQ 4%	Cream	Nightly	$	Epidermal	None				Exogenous Ochronosis
TCC	Cream	Nightly	$$	Epidermal	None		++	+	Exogenous Ochronosis
Tretinoin	Cream	Nightly	$	Epidermal	None		++	+	
Adapalene	Cream	Nightly	$$	Epidermal	None		+	+	
GA Peel	Peel	Monthly	$$	Epidermal	1-2 Days	+	++	+	
TCA Peel	Peel	Monthly	$$	Epidermal and Basal	2-3 Days	++	+++	++	Exfoliation
Picosecond Nd:Yag	Laser	Monthly	$$$	Epidermal and Basal	1-2 Days	++	+++	++	
Q switched Nd:Yag	Laser	Monthly	$$$	Epidermal and Basal	1-2 Days	++	+++	++	
Nonablative fractional	Topical	Monthly	$$$	Epidermal and Basal	1 Week	+++	+++	+++	Exfoliation
Intradermal Transamin	Injectable	Monthly	$$$	Epidermal and Basal	1 Day	+++	++	+	Haemostatic Disorder

Primary Care Recommendations

As established in numerous studies, combination therapy is superior to monotherapy in the treatment of melasma. Under ideal circumstances, the optimal treatment protocol for melasma includes the use of triple combination cream, low fluence picosecond Nd:Yag, and intradermal transamin in a multimodality approach to reduce production and enhance elimination of melasma.

The triple combination cream should be applied lightly to affected areas nightly for a maximum duration of two months. Thereafter the patient is transitioned to adapalene gel 0.1% nightly for maintenance. If necessary, the triple combination cream can be restarted after a two-month break.

Low fluence picosecond Nd:Yag is prescribed monthly. Initial settings of 0.5 J/cm^2 10Hz 8mm should be used to tone the entire face for a total of 3 rounds. An extra round should be performed on affected areas. The total amount of shots should range from 2000-3000 depending on the size of the face and lesions. The fluence can be gently uptitrated as tolerated across sessions with the goal to achieve a slight erythematous hue upon treatment completion.

Intradermal transamin is also to be delivered monthly. This should be performed at the same session and immediately after the completion of laser treatment. A 34G needle can be used to intradermally deliver 1ml of 50mg/ml of transamin at 0.05ml per injection at 1cm intervals to the entire face with a focus on affected areas. The combination of laser therapy and intradermal transamin facilitates medication delivery and improves hydration. It also reduces clinic visits, lidocaine cream use, and post-treatment downtime.

Policy Recommendations

It would be a major achievement if policy makers were to petition for melasma to be included in major insurance coverage alike dermatological conditions such as rosacea. Its inclusion would directly benefit patients via an increase in access to care at the primary level. There would also be an indirect increase in research funding given the significant financial impetus associated with the sheer size of the population afflicted with melasma.

In the meantime, policy makers should remind the public to only seek medical care from licensed medical practitioners as unregulated use of medications or interventions can lead to irreversible adverse events such as exogenous ochronosis, burns, and haemostatic complications.

Conclusion

Melasma is a widespread and prevalent condition that tend to afflict darker skin tone women of childbearing age. It remains overlooked and undertreated despite its well-studied psychosocial effects.

Increased awareness towards the condition will generate more robust studies which in turn will lead towards more effective, accessible, and affordable treatments. Validated disease specific scales exist and should be used to document and track disease progression.

Current treatment options can be monotherapy or a combination of hydroquinone, triple combination cream, retinoids, chemical peels, laser therapy, and intradermal transamin. An in-depth discussion between provider and patient is necessary to establish the optimal treatment plan that takes into consideration the route of administration and its accompanying risks.

The optimal management under ideal circumstances consists of a combination of triple combination cream, laser therapy, and intradermal transamin so as to target melasma production and elimination via a multimodality approach.

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