Combining Topical Therapy With Procedures to Treat Hyperpigmentation Disorders

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Hyperpigmentation disorders are commonly encountered by dermatologists. These disorders most frequently include melasma, solar lentigines, and postinflammatory hyperpigmentation. Although topical therapy is the mainstay of treatment, the number of procedures available to manage these disorders continues to increase. However, published studies describing combinations of topical therapy and procedures used to treat hyperpigmentation disorders are lacking. In this article, we discuss the etiology of these disorders and current therapies, review the literature, and describe the rationale for combining topical therapy with procedures. Additionally, we report the results of combining topical therapy with procedures in patients with hyperpigmentation disorders.

The most common hyperpigmentation disorders include melasma, solar lentigines, and postinflammatory hyperpigmentation (PIH). In the United States, these disorders have primarily affected patients with darker skin, most frequently those of African, Hispanic, and Asian descent.[1,2] Although women make up the majority of patients seeking treatment for hyperpigmentation disorders, men have become a rapidly growing sector.[3,4] Hadler et al[1] noted pigmentary disorders as the third most common reason for African American patients to visit a dermatologist. Furthermore, 9% and 14.2% of dermatology visits for African American and Hispanic patients, respectively, were reported to be related to pigmentary disorders. In another study, hyperpigmentation was mentioned as one of the top 10 reasons for Hispanic patients to visit a dermatologist.[2] In many of these patients, hyperpigmentation may be psychologically problematic. Recently, several studies in the literature have discussed the social and cultural implications of these disorders and how they may negatively affect quality of life.[5-7]

Dermatologists have many options in treating hyperpigmentation disorders. Evidence in the literature supports the use of topical therapy, including hydroquinone, retinoids, mequinol, azelaic acid, and kojic acid.[8,9] Additionally, several trials describe the efficacy of procedures such as chemical peels, dermabrasion, microdermabrasion, and laser and light therapy.[10] Combining topical therapy with procedures may have a synergistic effect that provides greater efficacy than a topical therapy or procedure used alone.[8] For example, combination regimens may hasten results, aid in preventing posttreatment PIH, and accelerate healing time.[11-13] There are only limited studies in the literature reporting the use of topical therapy in combination with procedures to treat these disorders.

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MELASMA

Melasma is a common condition among women, although up to 10% of patients seeking treatment are men.[3] Melasma is characterized by brown to blue-gray macules and patches with well-demarcated borders. The most common site affected is the face, although the dorsal arms and presternal areas also can be involved. Individuals with darker skin (Fitzpatrick skin type IV or higher), such as African American, Hispanic, and Asian patients, are at greater risk for developing melasma. Patients with lighter skin who live in areas of high UV radiation (UVR) also have a greater risk of developing this disorder. Genetic predisposition and hormonal shifts, as well as chronic overexposure to the sun, contribute to melasma, although the exact mechanism of development from these factors is unknown.[14] Women who are pregnant or taking oral contraceptives also have a high incidence of melasma.[15] Melasma in pregnant women tends to fade postpartum but generally returns with subsequent pregnancies.[16] In contrast, melasma secondary to oral contraceptive use typically does not fade after discontinuation of the drug and often takes several years to resolve. UVR exposure contributes to the development and exacerbation of melasma and increases melanin production and transfer, as well as the number of melanocytes.[17] The result is deposition of melanin in all epidermal layers and, in some cases, within the macrophages of the superficial and mid dermis.[18] Dermal involvement leads to cases that are refractory to traditional treatments. Melasma may negatively affect quality of life, especially in patients with refractory disease.[6,7] In these patients, topical therapy in combination with procedures may be the only effective means of improving the condition.

Multiple treatments for melasma have been reported in the literature and are commonly prescribed by most dermatologists. The most popular consist of topical therapy, such as hydroquinone, retinoids, mequinol, and low-potency corticosteroids.[8] These therapies are frequently compounded into various topical combination regimens; for example, hydroquinone combined with retinoids, glycolic acid, or both is described as beneficial in treating melasma.[10] In addition, the triple-combination cream of hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% has been approved by the US Food and Drug Administration and has been shown to be safe and effective in multiple melasma trials.[19-22] The liberal use of sunscreen with a sun protection factor (SPF) of 15 or higher is an important addition to any treatment regimen. Sunscreen helps prevent exacerbation and recurrence of melasma secondary to UVR during and posttreatment.

Procedures such as chemical peels, dermabrasion, microdermabrasion, and laser and light therapy have been reported as variably effective but remain controversial.[10] In patients with darker skin, special care is needed because of possible posttreatment PIH. Intense pulsed light (IPL) lasers, as well as Q-switched (QS) lasers such as the 1064-nm or frequency-doubled 532-nm Nd:YAG, the 755-nm alexandrite, and the 694-nm ruby have been reported to offer some benefit but must be used with caution to prevent dyspigmentation and scarring.[10] Combining QS lasers with ablative lasers, including both erbium and carbon dioxide, was reported to be effective in a study of 8 patients with melasma.[23] Recently, fractional laser therapy has been reported to be effective in treating recalcitrant melasma.[24,25]

A few reports in the literature describe combinations of topical therapy and procedures to treat melasma. Sarkar et al[26] reported that using hydroquinone 5%, tretinoin 0.05%, and hydrocortisone acetate 1% in combination with glycolic acid peels produced marked improvement in Indian patients with melasma when compared with topical therapy alone. In another study, using hydroquinone 2% in combination with glycolic acid 10% produced improvement in Asian patients with melasma compared with hydroquinone 2% alone.[27] Additionally, Lawrence et al[28] reported that superficial peels hastened the effects of topical hydroquinone 4% and tretinoin 0.05% in patients with melasma. Another study described the combination of topical hydroquinone 4% and IPL as effective in treating melasma and preventing PIH in 33 Asian patients.[29]

In our clinic, the combination of a series of glycolic acid peels every 3 weeks in addition to the triple-combination therapy of topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.1% has produced significant improvements in several patients (M.R., unpublished data, 2006-2007). Figure 1A shows a patient with significant melasma that was refractory to multiple topical therapies. The patient's melasma, a source of embarrassment and anxiety, negatively affected her quality of life. She underwent 3 treatments with the 532-nm QS Nd:YAG laser every 4 to 6 weeks along with daily application of the topical combination of hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%. There was marked improvement in hyperpigmentation over the entire face, most notably in the forehead region, at 6 months posttreatment (Figure 1B). The patient was happy with the results and noted an improvement in her self-esteem.

SOLAR LENTIGINES

Solar lentigines are light brown to black macules characteristically appearing on skin that is chronically overexposed to the sun. They are most commonly found on the face, shoulders, back, dorsal forearms, and hands. Unlike ephelides, lentigines do not resolve with reduced UVR

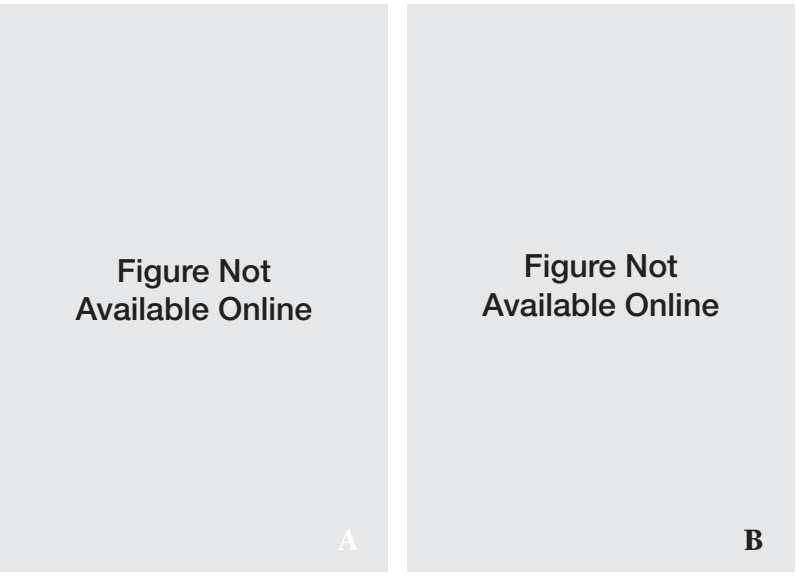

Figure 1. Patient with significant melasma before (A) and 6 months after (B) 3 treatments with the 532-nm Q-switched Nd:YAG laser every 4 to 6 weeks along with daily application of a topical combination of hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%.

exposure. Solar lentigines affect up to 90% of white individuals by age 60 years but are seen in all races.[9] Furthermore, an estimated 20 million Americans are affected by solar lentigines.[30] Chronic exposure to UVA and UVB radiation is implicated as the cause of solar lentigines. This theory is supported by the development of diffuse solar lentigines in patients on combination psoralen and UVA therapy.[31] The pathophysiology of solar lentigines includes increased melanin production and transfer to basal keratinocytes, as well as increased numbers of melanocytes. Along with the elongation of rete ridges, these are classic histologic findings.[32] Patients with multiple lesions have reported that their solar lentigines are a source of embarrassment and negatively affect quality of life.[5]

Topical therapies for treating solar lentigines include hydroquinone, retinoids, mequinol, and kojic acid.[9] Mequinol 2% and tretinoin 0.01% solution has been approved by the US Food and Drug Administration and is effective in treating solar lentingines.[33-35] As with melasma, the most important therapy in preventing solar lentigines is the consistent and liberal use of sunscreen. Broad-spectrum chemical sunscreens or physical blockers containing titanium dioxide or zinc oxide and with an SPF of 15 or higher are necessary to prevent the formation and worsening of solar lentigines.

Common procedures for treating solar lentigines include cryotherapy (liquid nitrogen), chemical peels, dermabrasion, microdermabrasion, and laser and light therapy.[9] With these procedures, it is important to note the risk of posttreatment hypopigmentation. This occurs with destruction of melanocytes that are involved in the active production of melanin. Additionally, peripheral hyperpigmentation with cryotherapy can be seen when the active periphery of a lesion is treated less aggressively than the center. A cryotherapy temperature of −4°C to −7°C has proven to be successful in destroying melanocytes and improving the appearance of solar lentigines.[9] A thaw time of 1 to 2 seconds ensures that posttreatment hypopigmentation does not occur.[30] Recurrence rates of solar lentigines have been estimated at up to 55% at 6 months postcryotherapy.[9] Although cryotherapy has traditionally been the most common procedure for treating solar lentigines, Todd et al[36] reported that the frequency-doubled QS Nd:YAG laser was the most effective procedural treatment. Other noteworthy lasers and lights for treating solar lentigines include pulsed dye, QS ruby, QS alexandrite, diode, and IPL.[37]

Several combinations of topical therapies and procedures used to treat solar lentigines have been described in the literature. The use of mequinol 2% and tretinoin 0.05% solution in combination with cryotherapy has been shown to be effective in treating solar lentigines.[30,33] Additionally, this combination has been shown to reduce PIH, which may result from cryotherapy alone.[34] In a study by Farris, [37] mequinol 2% and tretinoin 0.05% solution in combination with trichloroacetic acid peels and cryotherapy resulted in improvement of 90% or better in half the patients studied. Stough and Dugan[30] reported positive results with this combination as well; 64% of the patients reported "very satisfactory" results when compared with baseline.

In our clinic, a patient presented for treatment of solar lentigines of the left cheek (Figure 2A). The treatment regimen included daily application of topical mequinol 2% and tretinoin 0.05% solution along with 2 IPL laser treatments 4 weeks apart. There was marked overall improvement in the appearance of solar lentigines 6 months posttreatment (Figure 2B). The patient in Figure 3A complained of solar lentigines overlying the left temple. This patient underwent 1 treatment with the 532-nm QS Nd:YAG laser and daily application of triple-combination therapy of topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%. There was significant improvement of the lentigines at 6 months posttreatment (Figure 3B). Additionally, we have had positive results in treating acral solar lentigines with the daily application of hydroquinone 4% cream in

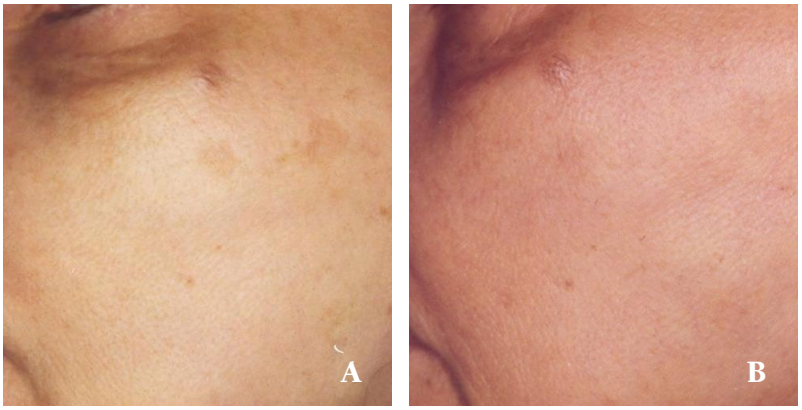

Figure 2. Patient with solar lentigines of the left cheek before (A) and 6 months after (B) treatment with daily application of topical mequinol 2% and tretinoin 0.05% solution and 2 treatments with intense pulsed light lasers 4 weeks apart.

combination with 1 treatment of the LightSheer™ diode laser. In contrast to melasma, solar lentigines seem to be most effectively treated with the combination of topical therapy and laser therapy. If lasers are not available, cryotherapy or trichloroacetic acid peels combined with topical therapy are effective alternatives.

POSTINFLAMMATORY HYPERPIGMENTATION

PIH generally occurs secondary to inflammatory lesions, photoinduced dermatoses, surgery, and trauma, but may also result from cosmetic procedures. It can occur in patients of all races and ages, but is most prevalent in patients with darker skin. There is no gender predilection associated with developing PIH. The visual appearance of hyperpigmentation may last for several months to years after the initial traumatic insult takes place.[38] The increased pigment can be attributed to increased melanin synthesis and transfer to keratinocytes. The basement membrane becomes disrupted, resulting in melanin incontinence in the dermis, which accounts for the longevity of the pigmentary alteration. Hemosiderin deposition from hematocyte extravasation is an additional factor behind PIH.[18] The resulting hyperpigmentation may concern patients, leading to embarrassment and anxiety in social settings, thereby negatively affecting quality of life.[5,38]

Topical therapies are the mainstay treatment for PIH and are similar to those used for other hyperpigmentation disorders. These therapies include hydroquinone, retinoids, mequinol, azelaic acid, and low-potency corticosteroids.[39-41] As with therapy for other hyperpigmentation disorders, therapy for PIH must include a broad-spectrum sunscreen applied daily to prevent worsening of the condition.

Procedures in combination with topical therapy may be useful in treating PIH. The dermatologist must use caution when treating any hyperpigmentation disorder with procedures such as IPL therapy, laser therapy, chemical peels, and dermabrasion, as these may lead to the development or worsening of PIH.[29,42,43] Manaloto and Alster[44] reported PIH in several patients who underwent Nd:YAG laser treatment for melasma; use of glycolic acid peels and topical azelaic acid resulted in improvement of PIH in these patients. Chemical peels, alone or in combination with topical therapy, have been reported to be successful in treating PIH.[17,38,39] In fact, Roberts[42] described chemical peels as the treatment of choice in hyperpigmentation disorders affecting patients with darker skin. Grimes[45] noted an improvement of PIH using salicylic acid peels in combination with topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%. Additionally, Stratigos and Katsambas[39] described the benefit of glycolic acid peels in combination with topical hydroquinone 4%, tretinoin 0.05%, azelaic acid 15%, and kojic acid 4% for treating PIH.

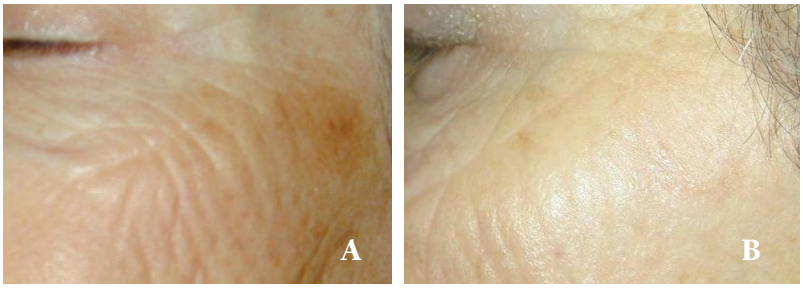

Figure 3. Patient with solar lentigines overlying the left temple before (A) and 6 months after (B) 1 treatment with the 532-nm Q-switched Nd:YAG laser and daily application of triple-combination therapy including topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01%.

The patient in Figure 4A had PIH secondary to severe acne vulgaris. The resulting hyperpigmentation was very upsetting for the patient, causing her to avoid social functions. The patient underwent glycolic acid 30% peels in combination with topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% cream. There was a dramatic improvement in PIH, most notably over the forehead and perioral regions, 6 months posttreatment (Figure 4B) and notable improvement in the patient's emotional disposition at the follow-up visit.

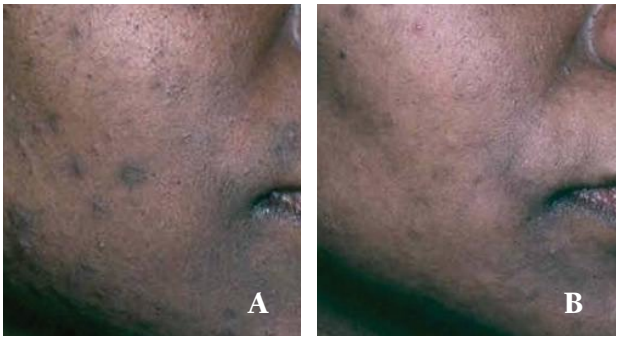

Figure 4. Patient with postinflammatory hyperpigmentation secondary to severe acne vulgaris before (A) and 6 months after (B) treatment with glycolic acid 30% peels in combination with topical hydroquinone 4%, tretinoin 0.05%, and fluocinolone acetonide 0.01% cream.

COMMENT

Using a combination of topical therapy and procedures to treat hyperpigmentation disorders is logical, especially in recalcitrant conditions. The evidence base for these combinations is lacking, with most treatments consisting of topical therapy or procedures alone. In general, where trials exist, there is evidence to support combining topical therapy and procedures. Combination regimens may lead to more rapid, greater improvement of hyperpigmentation and, when used properly, may lessen the risk of PIH. There are numerous combinations of topical therapy and procedures that may prove effective in treating hyperpigmentation disorders.

Eighty percent of the world's population is described as having ethnic skin, which has a higher risk of developing hyperpigmentation disorders.[1] These disorders may negatively affect patient quality of life. The safety and efficacy we have observed from treating our patients with a combination of topical therapy and procedures adds to the growing evidence supporting these treatments. Increased clinical trials researching effective combinations of topical therapy and procedures are needed to further support the findings presented in this article.

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