Combination therapy in skin of color including injectables, laser, and light devices

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Abstract
With the rapid increase in patients seeking cosmetic treatments, the variation in responses of lightly pigmented skin versus darkly pigmented skin has become increasingly apparent. Despite extensive treatment options in patients with skin of color, there is a paucity of well-designed studies performed in this patient population. The lack of research is concerning, as it is well documented that patients with darker skin types are at an increased risk of adverse events when treated with many of the available modalities used in cosmetic procedures. Fortunately, by combining a variety of treatments, these risks may be abrogated, and combination treatments may be a promising regimen for a wide variety of cosmetic complaints. An overview and evaluation of the research of combination therapy in skin of color is presented.

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Thus, many recent studies have begun to investigate the benefits of combining procedures and treatments to maximize benefits while decreasing the risk of adverse events.

Face
Melasma
Melasma, an acquired disorder of hyperpigmentation, is one of the most common types of pigmented lesions found in patients with skin of color. Though its exact cause is unknown, melasma is exquisitely photosensitive and exacerbated by hormones. Traditional treatment has typically relied upon strict physical sunblock use in conjunction with a topical combination of tretinoin, hydroquinone, and a topical steroid. However, although a topical cream may lighten epidermal pigment, it does little to alleviate pigment centered in the dermal layer of the skin. Additionally, prolonged use of topical hydroquinone may cause paradoxical hyperpigmentation due to exogenous ochronosis, and irritation secondary to topical retinoids may induce skin irritation, increasing the risk of PIH.

Thus, lasers have been investigated for efficacy in treatment of melasma given their potential to reach deeper depths in the dermis. In order to bypass epidermal pigment, several studies have attempted pretreating with an ablative laser to remove the epidermis, thereby decreasing intervening epidermal pigment between a Q-switched (QS) laser and dermal pigment. Angsuwarangsee et al treated 6 Thai patients with an ultrapulse carbon dioxide (CO2) ablative laser to one side of the face followed by a QS alexandrite 755-nm laser to the entire face. Six months following the procedure, the side of the face with combination treatment had significant lightening. There was no significant reduction of pigment on the side of the face treated with a QS alexandrite laser alone. Notably, when the 2 sides were compared directly, the difference in treatments did not reach statistical significance. Additionally, those patients with Type IV-V skin required a topical bleaching agent 3 months after their laser treatment to address their PIH. However, the relative success of the combination approach confirmed similar findings found using a pulsed CO2 ablative laser followed by a QS alexandrite laser. All 4 patients studied had improvement with the combination treatment, and no PIH was noted. A combination of intense pulsed light (IPL) followed by a QS 1064-nm Nd:YAG fractionated laser also had a significant lightening effect in patients with Type III-IV skin with no PIH noted. The authors hypothesized that the success of the treatment relied on the large action spectrum of the 2 lasers, with IPL covering epidermal pigment and dermal pigment covered by the QS Nd:YAG.

Low fluence QS Nd:YAG alone can successfully treat melasma; however, numerous weekly treatments are needed, and postprocedure hypopigmentation has been documented. However, when treated with 5 sessions of IPL immediately following low fluence QS Nd:YAG, 14 out of 18 patients rated their response as good to excellent.

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excellent, and only 1 patient developed guttate hypomelanosis. Treatment numbers with low fluence QS Nd:YAG may also be lowered by pretreating initially with microdermabrasion. When 27 women were treated with microdermabrasion followed immediately by QS Nd:YAG, the mean number of monthly treatments was only 2.6, and 85% of women experienced a 75% or greater improvement in their melasma. Additionally, a more recent split-face study compared a QS 1064-nm Nd:YAG laser with a QS 755-nm alexandrite laser using very low fluences of only 1-2 J/cm² for the treatment of melasma. In 18 patients with types III and IV skin, pigmentation improved equally well on both sides of the face after 6 weekly treatments, and there were no adverse events aside from minimal transient erythema. Thus, though using very low fluences requires multiple treatments, it does appear to minimize the risk of dyschromia while still maintaining efficacy.

Perhaps because laser and light treatments can be manipulated to very narrowly target melanocytes in different layers of the skin, combinations of these treatments appear to work better than combination treatments of lasers with topical treatments such as chemical peels. When 30% glycolic acid peels were added to low fluence QS Nd:YAG laser sessions, 15 male patients with melasma were found to have only transient improvement, and 1 patient developed permanent guttate hypomelanosis. Thus, combination laser treatment does appear to be a viable option in patients with melasma unresponsive to topical treatment alone.

In our practice, a combination of IPL (560-nm filter) and 755-nm picosecond laser (Picoseure, Cynosure, Inc, Westford, Massachusetts) or 755-nm QS laser (Accolade, Cynosure, Inc, Westford, Massachusetts) in conjunction with topical treatments has been utilized to successfully treat a skin type III patient (Figure 1). The 35-year-old female suffered from severe melasma refractory to conventional topical therapy and sun protective measures, and

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remaining pigment in the previously treated areas as well as the pigment on the lower eyelid. To date, 2 treatments with the 1064-nm picosecond laser (PicoWay, Syneron Candela, Irvine, California; fluence ranging from 3.0-3.2 J/cm², 4-mm spot size, 3-4 Hz) and 1 treatment with the 755-nm picosecond laser (fluence of 2.08 J/cm², 3.5-mm spot size, 10 Hz) have been performed following placement of internal metal eye shields. At this time, the patient remains in follow-up every 6-8 weeks with additional picosecond laser treatments planned to target remaining pigment.

Nevus of Ota is rarely the only etiology of dyspigmentation on the face. Patients often have concurrent pigmentary lesions, such as melasma, pigmentated seborrheic keratoses, ephelides, or lentigines, and thus may be classified as having complex dyspigmentation. Park et al attempted to combine global photorejuvenation with targeted pigment therapy by beginning with IPL therapy and following with 694-nm QS ruby laser in 25 Korean patients with at least 2 pigimentary disorders, and 4 of whom had acquired Nevus of Ota; 60% experienced a 75%-100% improvement as assessed by 2 independent dermatologists. Three patients had transient PIH that resolved with subsequent IPL treatments, and 1 patient had PIH.21 As the incidence of PIH can be high regardless of the laser used, the authors commonly perform a test spot to assess skin reaction and clearance from the treatment prior to treating the entire area.

Acne scars
Severe acne can have a significant deleterious impact on quality of life. Without adequate treatment, the scarring and pigmentary changes may persist indefinitely despite clearance of the acne itself. Therefore, acne and acne scarring are common complaints in patients seeking dermatologic treatment. Several types of scars may develop after acne through dermal fibrosis or pigmentary alteration, and treatment of the scars is challenging, as more hypopigmentation or scarring may occur. Additionally, multiple types of lesions may be contributing to a patient’s undesired appearance. For example, it is not uncommon to have both an inflammatory and scarring component at the same time. Thus, severe acne and acne scarring may be better treated with multiple modalities able to target the underlying lesions most effectively.

Though isotretinoin is often effective and first line, many patients cannot tolerate the excessive dryness or develop one of the rarer, severe side effects. Topical 5-aminolaevulinic acid-photodynamic therapy (ALA-PDT) has long been used for treatment of actinic keratoses but has also shown efficacy for treatment of acne and is safe in patients with pigmented skin.22,23 By using a combination of both ALA-PDT treatment with an ablative fractional Er:YAG 2940-nm laser in 40 patients with skin types III-IV, Yin et al showed complete resolution of all active acne lesions after 4-5 monthly sessions and no new scars. Six months following the last treatment, 80% of subjects’ scars improved by more than 50%, and 25% of scars improved more than 75%. A third of patients developed transient PIH, though all improved by 6 months.

In our practice, we routinely use a combination of ALA-PDT and pulsed-dye laser (PDL) for treatment of active acne and erythematous acne scars. In certain cases, IPL is also incorporated into the regimen. ALA is applied to the face after extractions and exfoliation with a vibrating microdermabrasion system (Vibraderm, Grand Prairie, Texas) are performed. It is then degreased with an acetone wash. Figure 3 demonstrates a 22-year-old skin type IV female treated with subpurpuric full-face PDL to activate the photosensitizer followed by simultaneous illumination with a blue light (Blu-U, DUSA Pharmaceuticals, Inc, Wilmington, Massachusetts) source positioned 50 to 50 mm from the skin for an illumination period of 16 minutes 40 seconds, light dose 10 J/cm², and a red light source (Aktilite CL 128, PhotoCure ASA, Oslo, Norway) positioned 50 to 80 mm from the skin for a total of 8 minutes, 49 seconds at a standardized fluence of 37 J/cm². Incubation with ALA was 3 hours prior to treatment. The patient was prescribed oral spironolactone (50 mg twice daily) and instructed to use topical benzoyl peroxide as needed for spot treatment, as she could not tolerate daily treatment over her entire face. At the 3-month follow-up, greater than 75% clearance was noted. The patient has continued her oral and topical medications with additional PDL treatments planned as needed, and fractional CO2 resurfacing has been recommended as part of her combination treatment plan.

In a pilot study in which 22 subjects (Fitzpatrick Skin Types IV-V = 9/22) received 3 treatments 14 days apart with microfocused ultrasound (MFU-V) using the 1.5-mm, 10-MHz (300 total lines to the entire face) and 1-mm, 10-MHz (420 lines to the entire face) depth transducers, a significant decrease in sebum, as measured by a sebumeter (Courage-Khazaka, Köln, Germany), was noted over the forehead, cheeks, and chin 60 days post treatment. Eighty percent of subjects had a decrease in total acne lesion count at 60 days, and 100% of subjects showed a decrease at 180 days after the last treatment. It is hypothesized that, with the use of 1.5-mm and 1-mm depth probes, sebaceous glands are targeted for coagulation while bypassing the basal layer. Data from this pilot trial suggest that MFU-V could prove to be a promising novel treatment option to improve acne clearance in those with moderate to severe inflammatory acne. An additional study found that 20 patients (75% of whom had skin type III or above) all noted improvement of their atrophic acne scars following 3 monthly sessions of MFU-V.

In a Chinese study, 37 patients with both atrophic scars and in...
In our practice, fractionated ablative and nonablative lasers are routinely used for rejuvenation of facial photodamage in skin types III-V in combination with other lasers, injectable fillers and neuro-modulators, and medical grade lightening products. The skin type IV patient in Figure 4 presented as an anti-aging consult, most concerned about the lentigines, volume loss, and overall photodamage on her face. On the same day, the patient underwent treatment with a soft tissue filler for the cheeks and chin (Radiesse, Merz, Raleigh, North Carolina) and a QS 755-nm alexandrite laser to target individual pigmented macular seborrheic keratoses, immediately followed by a 1927-nm fractionated thulium laser to the full face, followed by neuromodulator injection 2 weeks later.

**FIGURE 4.** A 5-year-old skin type IV female with facial photodamage. (A) Baseline; (B) 12 months status post soft tissue filler for the cheeks and chin, and a QS 755-nm alexandrite laser to target individual pigmented macular seborrheic keratoses, immediately followed by a 1927-nm fractionated thulium laser to the full face, followed by neuromodulator injection 2 weeks later.

Facial photodamage and rejuvenation

The conditioned medium of ADSCs has also been used immediately following fractional CO2 laser when treating facial photodamage in skin types III-IV. Because the laser forms microscopic holes in the skin, drug delivery is hypothesized to be significantly enhanced. Thus, the growth factors in the ADSC medium should be able to more efficiently recruit dermal fibroblasts and increase dermal collagen. In fact, histologic analysis of the subjects’ skin showed increased dermal collagen density and more ordered collagen than the facial side treated with laser alone.

For noninvasive treatment of facial wrinkles, a combination of optical energy with RF or heat energy are thought to work synergistically with each other. First, the optical energy specifically heats a target, which then further concentrates the heat energy administered by the RF device. Twenty-three patients were treated for facial and neck wrinkles with up to 3 sessions of a combination diode laser and RF system (Polaris, Syneron Medical Ltd., Yokneam, Israel), after which 30% experienced at least a 50% improvement and 66% noted at least a 25% improvement, with no reports of pigmentedary change. Patients had skin prototypes ranging from II to IV, though there were no notable differences in efficacy based upon skin type.

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bad, California). Future treatment with additional filler and MFU-V for skin tightening has been recommended as part of her ongoing combination treatment plan.

**Neck**

**Skin laxity**

Due to ultraviolet radiation damage and chronological aging, dermal collagen and elastin gradually diminish, resulting in skin laxity, which may be particularly pronounced over the neck.\(^4\) For superficial skin tightening, fractionated ablative CO2 laser has been shown to improve neck laxity by an average of 57% at 2 months.\(^4\) However, as noted above, even fractional CO2 treatment of patients with pigmented skin carries a high risk of PIH.\(^2\) Newer devices utilizing radiofrequency or ultrasound technology have become increasingly popular for treatment of off-face skin laxity.\(^3\) As neither radio nor ultrasound waves target pigment, their use in patients with darker skin types typically carries no greater risk than treatment for patients with less melanin.\(^1\) Additionally, ultrasound technology does not cause enough edema or erythema to interfere with subsequent laser applications and thus offers an attractive adjunct for the treatment of neck laxity.\(^4\) In 60 patients treated initially with microfocused ultrasound with visualization (Ulthera System, Ulthera, Inc, Mesa, Arizona) using the 4.5-mm, 4-MHz; 3-mm, 7-MHz; and 1.5-mm, 10-MHz transducers at the highest energy settings delivering the number of lines based on manufacturer protocol followed immediately with treatment by an ablative fractionated laser, the improvement in skin laxity and texture of the neck was thought to be greater than the physicians’ prior experience using either modality alone. The recovery time was delayed an additional 3 to 4 days, though the incidence in other adverse events was not noted. However, this article did not specify the skin types of the patients studied.\(^4\) Yet, when MFU-V was studied in 52 patients with skin types III-IV for tightening of the skin of the face and neck, the only prolonged adverse event noted was erythema in 1 patient.\(^4\)

If a patient wishes to address both pigmented change in addition to skin tightening, Vanaman et al recommend beginning with a vascular laser, either IPL or PDL, then using tumescent anesthesia prior to subsurface monopolar RF (ThermiTight, ThermiAesthetics, Irving, Texas), and completing the session with a QS 532-, 694-, or 755-nm laser for any remaining pigmented lesions. As the 3 devices all have very different targets, no increased scarring or adverse events were noted.\(^4\)

**Body**

**Cellulite**

Though affecting up to 80% of postpubertal women, cellulite remains a very difficult condition to treat, particularly using non-invasive technologies alone.\(^4\) However, the combination of mechanical manipulation, infrared light, and RF does show promise. Seven patients with skin phototypes ranging from III-IV for tightening of the skin of the abdomen and 50% on the thighs.\(^4\) Patients experienced an average of 25% improvement of cellulite on the abdomen and 50% on the thighs.\(^4\) The only adverse event reported was a single blister, which healed without scarring. Though the improvement was moderate at best, combination therapy using heat and mechanical stimulation does appear to be effective and safe for the treatment of cellulite in pigmented patients.

More recently, a subcision approach (Cellfina System; Ulthera Inc, Mesa, Arizona) has been described that manually dissects the fibrous network causing dimpling in the dermis. A precise depth of dissection may be fixed through a vacuum chamber to lift the tissue for the needle. As the Cellfina is a non-energy-based device, it is an attractive treatment option for patients with pigmented skin. Seventy-eight percent of patients enrolled in the original trial were skin type III and above, and 33% of patients had skin type IV or above. Every subject noted an improvement at 1 year, and no long-term adverse events or PIH were recorded.\(^4\)

**Scars**

Hypertrophic scars and keloids are quite common in skin of color patients and represent an exuberant healing response to trauma, inflammation, or burns.\(^3\) In addition to psychological distress caused by the appearance, keloids may also provoke sensations of pruritus or pain.\(^5\) Though numerous treatments have been proposed to improve the appearance and symptoms, keloids are notoriously recalcitrant or slow to respond to more conservative treatments such as intralesional steroid injections. Additionally, dyspigmentation and atrophy often accompany any improvement in the texture of the keloid. Unfortunately, keloids often recur, occasionally even growing to a larger size, after more aggressive or destructive techniques. By using a combination approach with a 578-nm copper bromide laser to target the vascular component of the scar in addition to intralesional triamcinolone acetonide, keloids were noted to improve by at least 50% in 9 of 12 treated Korean patients when assessed by 2 physicians blinded to the treatment protocol.\(^5\) The increased improvement over injections alone was hypothesized to occur secondary to thermal injury to the scar microvasculature, which then induced ischemia and collagen reduction.\(^5\) The authors also noted significantly less purpura following the laser treatments than would be expected to occur when using a PDL.

Yan et al specifically studied 151 symptomatic keloids, which had been present for greater than 2 years, were greater than 2 cm\(^2\) in size, and had failed treatment with 2 or more treatment modalities, including excision, laser, cryotherapy, pressure garments, and radiation. Keloids were first treated with continuous-wave CO2 laser followed by ultra-pulse CO2 laser 5-7 days later in order to prevent the proliferation of scar tissue. Following the second CO2 treatment,\(^2\) P-patch contact brachytherapy was performed. One hundred and eleven of the keloids responded without a noticeable scar or a cosmetically satisfactory scar following treatment, and 40 of the keloids resolved into a hypertrophied scar. None of the keloids were rated as being as large or larger than baseline following treatment, though approximately 50 treated sites were notable for residual hyperpigmentation or depigmentation.\(^5\) Thus, for particularly recalcitrant keloids, a combination therapy using both laser and radiation may provide significant benefit.

**Striae**

Striae distensae is a common cause of cosmetic concern characterized histologically by thinning of the epidermis as well as dermal collagen and elastin.\(^6\) If the striae are erythematous, the pigment may be treated safely in individuals with pigmented skin with a
585-nm dye laser, though the textural change is much more difficult to improve. More recently, a microneedle RF device (INTRAcel, Jeisys, Seoul, South Korea) has been shown to improve numerous dermal abnormalities such as rhytides, scars, and keloids. The textural improvement is thought to occur through wound remodeling and tightening in response to heat-induced collagen denaturation. With the combination of both RF technology (Thermage, Solta Medical, Inc, Hayward, California) and a 585-nm PDL, almost 90% of Asian patients noted an overall improvement in their striae, with approximately 60% showing “good or very good” improvement in the elasticity of their striae. In 10 patients with skin type IV, the combination of fractional CO2 laser with microneedle RF (Secret; illooda, Suwon, South Korea) showed greater improvement in their striae than 20 patients treated with either fractional CO2 laser or microneedle RF alone, with transient PIH occurring in 30% of patients in the combination group versus 20% in each of the other 2 groups. Thus, combination treatment was shown to be more effective without significant increase in adverse events in treatment of striae.

At our site, we have an ongoing split-body comparison trial to evaluate the efficacy of a nonablative fractionated 1565-nm laser (ResurFX, Lumenis Ltd, Santa Clara, California) and combination 1064-/532-nm fractionated picosecond laser (PicoWay Resolve, Syneron Candela, Irvine, California) in the treatment of striae. Skin types I-IV have been treated. Subjects receive 3 treatments spaced 3 weeks apart. Preliminary data reveal comparable efficacy between the laser treatments; however, there is more discomfort associated with the 1565-nm laser. In addition, PIH lasting longer than 1 month has been observed in the majority of subjects on the sides treated with the 1565-nm wavelength, whereas long-lasting PIH has not been appreciated on the sides randomized to the picosecond laser. Final data will be available later this year.

Conclusion

With each year, new medical, injectable, surgical, and device-based therapies, used alone or in combination, are reported in the pursuit of treating skin of color safely and successfully. The efficacy of combined regimens (“mega-combinations”) is gaining popularity and is likely the future of treating most skin conditions to achieve optimal cosmesis. Additional research of combination treatment will be necessary to document safety, to quantify the benefits, to establish the duration of effects, to review cost-effectiveness, and to evaluate the psychological improvement and quality of life for patients using the various treatment modalities.

References


