Laser Treatment of Hypopigmentation in Scars: A Review

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BACKGROUND Despite history of multiple treatment modalities, repigmentation of hypopigmented scars remains a difficult clinical problem.

OBJECTIVE The purpose of this review is to evaluate the literature on laser and combination laser plus adjunct topical therapy for hypopigmented burn and traumatic scars.

MATERIALS AND METHODS A search on PubMed and on Oxford Academic was conducted with additional relevant literature obtained from reference lists.

RESULTS Treatment regimens that address hypopigmentation within scars were reviewed. A combination of nonablative fractional or ablative fractional laser treatment with topical prostaglandin analogue with or without topical retinoid were found to result in superior repigmentation.

CONCLUSION Reliable improvement of hypopigmentation in scars after laser treatment is challenging. Laser can achieve success in some cases. Ultraviolet laser can achieve modest repigmentation; however, results are short-lived and require continued re-treatment. Modest improvement in pigmentation is seen with nonablative fractional laser or ablative fractional laser alone and enhanced repigmentation is demonstrated when combining fractional laser resurfacing with topical application of synthetic prostaglandin analogues and other known modulators of melanogenesis.

Many patients seek treatment for scars.[1] Treatment is sought for a many reasons including symptoms of pain or burning, contractures limiting motion, and for amelioration of disfigurement including color mismatch between the scar and surrounding skin. Scars also can have lasting negative psychosocial effects, as they serve as reminders of the traumatic events which caused them.[2]

Treatment of cutaneous scarring has improved dramatically over the past decade with the use of fractional lasers.[3] However, hypopigmentation within scars remains very difficult to treat.

Pathophysiology of Scar Hypopigmentation

The 3 phases of normal scar formation can take 1 year to complete and can be influenced by multiple factors that result in pathological scarring, such as hypertrophy, keloid formation, and dyspigmentation.[3] Young age and darker skin type can contribute to the development of pathological scars. Hypopigmentation within scars is usually present throughout initial scar development, but it can also appear after time through a mechanism that is poorly understood.[4]

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Melanocytes are lost if the basal epithelium is destroyed. Partial-thickness burns heal when basal keratinocytes from the edge of the wound migrate over the surface. Migration is thought to only occur up to 1 inch from the edge of the burn.[5] Because newly synthesized epithelium consists of keratinocytes and not of melanocytes, it lacks pigment. After about 1 month, melanocytes can start to repopulate basal layers of epithelium by migrating from adjacent normal tissue. Hair follicle melanocytes are also thought to synthesize melanin, which is distributed in melanosomes to neighboring keratinocytes.[5]

Previous studies reported the absence of melanocyte migration in full-thickness wounds,[6] and it was thought that scar hypopigmentation resulted from complete loss of melanocyte activity, either due to failure of migration or due to loss of function. However, recent work by Carney and colleagues[7,8] in a porcine model and in human burn subjects revealed that melanocytes are present in equal amounts in hypo- and hyperpigmented regions within a full-thickness burn scar, even when nearby adnexal structures are absent.

Recent work of Carney and coworkers also show that the initial trigger in scar dyspigmentation is not DNA damage in the melanocyte itself, but rather due the lack of downstream modulators of melanin production, such as proopiomelanocortin. Proopiomelanocortin and its associated downstream effectors, adrenocorticotropin-releasing hormone and α-melanocyte stimulating hormone, are downregulated in hypopigmented regions.[8] This finding suggests that melanocyte activity is dependent on numerous signaling molecules, some of which are absent after traumatic and burn scarring but that may be replaced to stimulate pigmentation.[8]

Treatment Options

Nonlaser treatment for hypopigmentation in scars includes conservative therapy, excisional scar revision surgery, split-thickness grafting, medical tattooing, microneedling, and melanocyte-keratinocyte transplantation procedure.[9,10]

Conservative management, such as compression, silicone sheeting, and massage, have been standard in the treatment of burn and other traumatic scars and improve scar thickness, erythema, and texture.[1,3] Massage has been shown to sometimes improve hyperpigmentation in scars,[11] but conservative therapy generally does not address scar hypopigmentation.

Excisional scar revision surgery is often required when there is significant tension or webbing, and it addresses hypopigmented areas only by entirely removing the scar.[12] Split-thickness grafting requires harvesting skin from a donor site, which risks infection, further scarring, and dyspigmentation.[13] Medical tattooing uses a microsurgical needle to deposit skin-colored ink into scars in attempt to achieve uniform pigment. Risk of adverse effects is low, although reactions to tattoo dyes can occur, and outcomes are variable. Color mismatch can occur, especially as skin color may change over time, as with tanning.[9,14]

Microneedling or "medical needling" or "dry tattooing" involves rolling a device covered with 3- to 5-mm needles over the skin, inducing small areas of microtrauma to induce collagen formation. Microneedling does show some improvement in scar pigmentation; however, it has not been effective for large scars.[13] Busch and colleagues[13] demonstrated combination of microneedling and autologous cell transplantation, where microneedling is followed by spray suspension of viable autologous skin cells to produce both subjective and objective improvements in scar hypopigmentation. Nineteen subjects with second- and third-degree hypopigmented burn scars were randomized to receive noncultured autologous skin suspension (NCASCS) after microneedling, microneedling only (positive control), or no treatment at all (negative control). Repigmentation was assessed at regular follow-up over 1 year by subjects and independent observer using the Patient and Observe Scar Assessment Scale (POSAS). Seventeen of 19 subjects responded to treatment. Patient surveys revealed statistically significant 50% improvement in pigmentation in the NCASCS plus microneedling group, and the observer survey revealed a 37.5% improvement in pigmentation. Scar melanin index was also measured using a light-emitting diode-based device that measures skin pigmentation. The NCASCS plus microneedling group showed 29.3% increase in scar melanin index, whereas the positive and negative control groups displayed no significant changes in melanin index. Of note, all patients were Caucasian, and Fitzpatrick skin type was not recorded. This technique is promising; however, NCASCS is not widely available and is expensive.

Melanocyte-keratinocyte transplantation procedure is a surgical technique involving the harvesting of donor site skin, which is digested with trypsin, made into a cell suspension, and applied to the hypopigmented area after microdermabrasion.[10] This option involves a specialized technique available at only a few centers and is invasive.

The advantages of laser therapy are wide clinical availability, improved repigmentation as compared with conservative management while still being minimally invasive, and success in treating large hypopigmented scars. Furthermore, laser surgery does not require a donor skin site for grafting.[1,3] In many cases, laser therapy can start as early as 2 weeks after initial wound formation, whereas it is advised to wait at least 3 months for surgical revision.[12,15] This review will evaluate the literature on laser and combination laser plus adjunct topical therapy for hypopigmented burn and traumatic scars.

Materials and Methods

A literature search was performed using PubMed electronic database prioritizing studies based on relevance to laser treatment of hypopigmentation in scars, clinical consensus, and publication date. Search terms included "hypopigmentation" and "scars" or "hypopigmented scars" and "laser" or "laser treatment." A Google Scholar search was also conducted using the search term "ablative fractional treatment hypopigmented scars." Reference lists revealed 2 additional sources. Disease processes known to cause hypopigmentation such as vitiligo or post-inflammatory hyperpigmentation (PIH) were excluded. A total of 10 sources were included.

Results

Laser Treatment of Scar Hypopigmentation: Ultraviolet Light

The excimer laser, which emits 308 nm UV-B radiation, has long been used in the treatment of hypopigmented lesions such as vitiligo. A randomized study by Alexiades-Armenakas and colleagues in 2004[16] found a xenon chloride excimer laser (Xtrac [308 nm, 3.2 cm^2, 30 nanoseconds]; Photomedex, Radnor, PA) to be safe and effective in treating 22 patients with hypopigmented scars. Patients received 9 total treatments, twice weekly. Repigmentation was evaluated as percent pigmentation relative to uninvolved skin using visual assessment and colorimetric analysis. On average, scars achieved 61% repigmentation compared with uninvolved skin (95% confidence interval [CI], 55%–67%). Only transient erythema was reported as a side effect, which was a desired outcome to achieve proper laser dosing. However, ongoing treatment was required to maintain results, as it was noted for all subjects that scars regressed toward original hypopigmented state at 6-months follow-up. Although the study did not formally assess the longevity of results, it was noted that subjects with Fitzpatrick skin Types I to II may benefit from treatment every 1-to-2 months, and skin Types III to IV every 2-to-4 months.

Brandt and colleagues conducted a randomized control trial to treat 20 subjects possessing long-standing, hypopigmented facial scars with either microneedling followed by 320 to 400 nm UV-A light treatment or UV-A light alone.

Patients were evaluated at 7 months by an independent observer who utilized the Vancouver Scar Scale to assess scar vascularity, pliability, pigmentation, and height. Pigmentation within treated areas was measured using a reflectance spectrometer, which measures redness and melanin. Independent observer and patients rated overall satisfaction with 10-point scales. The microneedling plus UV-A treatment group displayed a statistically significant increase in melanin index, which approached that of surrounding uninvolved skin, and subjective patient and observer surveys also revealed statistically significant superiority in the microneedling group.[17] Of note, darker skin Types IV and higher were excluded. It is posited that microneedling, in addition to promoting tissue remodeling in the scar, also creates physical channels for melanocytes contained within the skin cells to transplant within the scar.

Fractionated Laser Systems

Fully ablative lasers such as the carbon dioxide (CO_2) and the erbium-doped yttrium aluminum garnet (Er:YAG) vaporize all tissue in a set area to a desired depth and have been studied since the early 1990s to improve hypopigmentation due to acne and surgical scarring on the face. However, these devices can induce hypopigmentation and must be used with caution. This is especially true with use on nonfacial body areas due to slower reepithelialization in adnexal-poor skin.[4,18] Fractional resurfacing was described by Manstein and Anderson in 2004 as a means to minimize side effects from fully ablative resurfacing and is much less invasive. Microscope thermal zones (MTZs) are columns of affected tissue. Nonablative fractional laser (NAFL) induces multiple zones of thermal coagulation, resulting in tissue remodeling (Figure 1). Ablative fractional laser (AFL) vaporizes columns of tissue from the epidermis into the dermis. Initially used for photorejuvenation, NAFL and AFL have been adapted for scar treatment and enabled safe treatment of scars on all parts of the body. It is theorized that fractional resurfacing induces repigmentation within scars through the creation of the MTZs, which provide paths for melanocytes and keratinocytes from normal surrounding basal epithelium to reach newly epithelialized scar tissue via a process termed the "melanin shuttle."[20–23]

According to a recent international consensus, 95% of scar treatment expert respondents suggest beginning treatment of hypopigmented scars with a fractionated laser[3]; however, consensus is split when deciding between NAFL and AFL: 56% of international consensus respondents opted for AFL.[3]

In 2007, Glaich and colleagues[21] treated hypopigmented acne and gas burn facial scars with a 1,550 nm laser using pulse energies of 7 to 20 mJ and total density of 1,000 to 25,000 MTZs/cm^2 per session for 2 to 4 treatment sessions every 4 weeks. Treatment response was assessed on a four-point scale by an independent physician evaluator who compared pre- and post-treatment photographs after each procedure. Follow-up 4 weeks after last treatment demonstrated improvements of 51% to 75% in scar hypopigmentation in 6 of 7 patients. Unfortunately, longer follow-up was not provided.

Pham and colleagues[24] described improvement in skin color match in Fitzpatrick Types I to III after 1,550 nm NAFL treatment of facial surgical scars. A total of 12 patients were treated. Treatment occurred every 4 weeks for a total of 4 treatments, with follow-up at 6 months. Laser settings were at physician's discretion, and details were not provided. An independent evaluator assessed scars while presented with a photograph from the previous visit for comparison. The evaluator scored the scar according to vascularization, pigmentation, pliability, thickness, and relief on a 10-point scale. Pigmentation rating by both subjects and independent physician evaluator achieved improvement in all but 1 patient, with $p < .001$. The patient (Fitzpatrick II) who reported no improvement in hypopigmentation was lost to follow-up prior to 6-months evaluation.

Choi and colleagues[25] compared 2 fully AFL treatments, 10,600 nm CO_2 fractional laser (CO_2FL) and 2,940 Er:YAG fractional laser, to determine efficacy in the treatment of hypertrophic scars. It was noted that hypopigmented scars showed some repigmentation after treatment, although no quantitative measure was captured to reflect this improvement.

In 2014, Kim and colleagues[26] enrolled 108 patients with surgical or traumatic scars and assigned groups one of two 10,600 nm CO_2FL devices, finding that pigmentation improved overall with a modified Manchester scar scale, demonstrating color mismatch score improving from 2.4 to 2.0 on average, where any value less than 6 is perfect. However, scar hyperpigmentation and erythema were the primary focus of this measure, and hypopigmentation specifically was not addressed. It was noted that approximately 6 subjects with normal or hypopigmented scars worsened treatment.

Laser-Assisted Drug Delivery

In 2010, AFL was adapted to enhance penetration of topical agents, such as prostaglandin analogues and retinoids.[27] Microscopic channels created by fractionated lasers allow for deeper penetration of drug moieties and even distribution into the tissue, creating a synergistic treatment strategy between laser therapy and topical agents.[28] Bimatoprost and latanoprost are synthetic prostaglandins that decrease intraocular pressure and have also been shown cause dose-dependent increase in pigmentation in periocular skin.[29,30] The mechanism behind induced melanogenesis is thought to be due to increased transfer of melanosomes from melanocytes to basal keratinocytes (Figure 2).[29,31] Topical retinoids, such as tretinoin, are also used as adjunct therapy for scar hypopigmentation by modulating tyrosinase activity.[29,32] Interestingly, retinoids are traditionally used to treat hyperpigmentation disorders, such as melasma and PIH, therough induction of apoptosis in mature melanocytes. However, in 2002, Watabe and colleagues[35] demonstrated that tretinoin can also increase pigmentation in the setting of hypopigmentation, possibly by inducing melanocyte differentiation and thus stimulating melanogenesis (Figure 2). Tretinoin may also aid in achieving a more even color appearance by normalizing melanin distribution.[29,32]

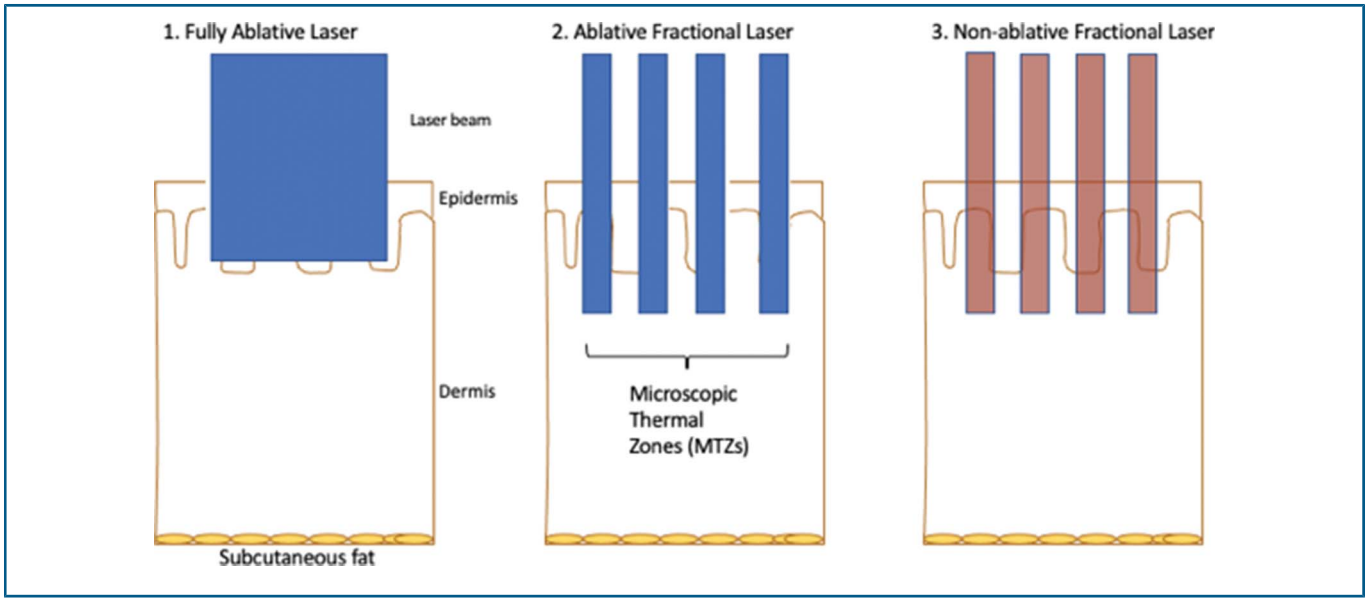

Figure 1. Schematic comparison between the effects of fully ablative, ablative fractional laser, and nonablative fractional laser on the skin.[19]

Topical calcineurin inhibitors, such as tacrolimus and pimecrolimus, which are commonly used in the treatment of vitiligo, are thought to aid in scar repigmentation by means of direct interaction between calcineurin inhibitors and keratinocytes.[29]

In 2012, Massaki and colleagues[29] demonstrated clinically significant improvement in all 14 patients with scar hypopigmentation using a fractionated 1,550 nm erbium-doped laser plus topical bimatoprost 0.03% twice daily for at least 3 months, and either daily topical tretinoin 0.05% starting 3 days after laser treatment or, if tretinoin intolerant, switching to topical pimecrolimus 1% cream. The number of laser treatment sessions ranged from 2 to 10 (mean 4.5) at 4- to 8-week intervals. Pulse energies ranged from 20 to 70 mJ and 20% to 30% density, starting with lower energies and increasing in subsequent visits. High pulse energies were utilized to increase penetration depth for optimum scar remodeling. An independent physician evaluator assessed clinical photographs taken before and after each treatment session and then again 4 weeks after the last treatment using a four-point scale. All patients returned for follow-up visits at 9 months after the last laser treatment session. Five of 14 patients had more than 75% improvement in hypopigmentation, and 12 had more than 50% improvement. All patients demonstrated prolonged results. Side effects were limited to transitory post-treatment edema and erythema (Figure 3).

In 2015, Siadat and colleagues[30] demonstrated that treatment with the 10,600-nm fractional CO_2 laser plus latanoprost 0.005% was superior to fractional laser alone. Twenty-eight patients of skin Types II to IV with hypopigmented scars were randomly divided into 2 groups. Group A received 6 sessions at 4-week intervals

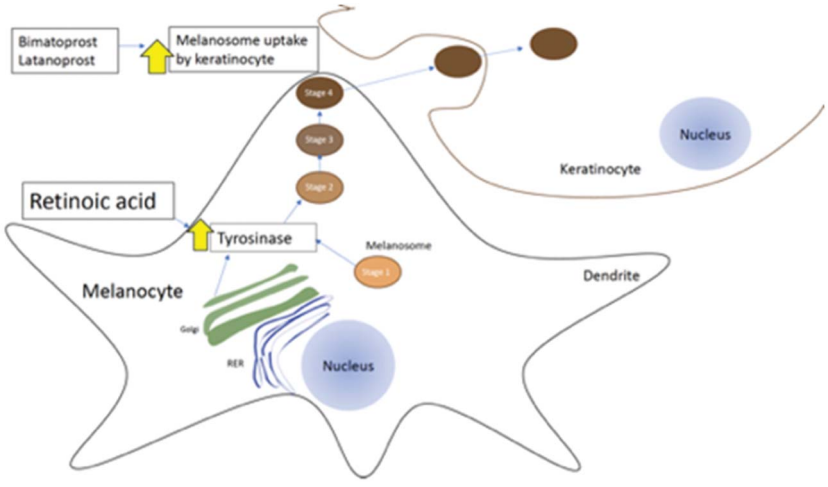

Figure 2. Proposed melanogenesis mechanism: topical prostaglandin analogues enhance melanosome uptake by keratinocytes, and tretinoin may induce melanogenesis via increased tyrosinase activity.[5,29,33,34]

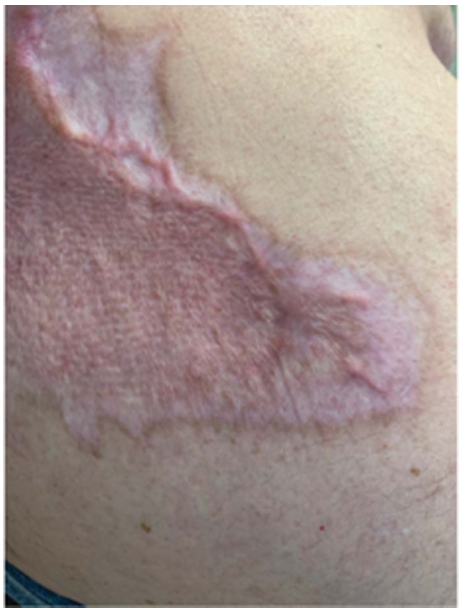

Figure 3. Hypopigmented scar.

with 10,600 nm fractional CO_2 laser plus topical latanoprost 0.005%, one drop over 2 × 2 cm area twice daily for 24 weeks. Group B received CO_2 laser plus saline placebo. Digital photographs were taken at baseline and at 3 months after last treatment. One blinded dermatologist compared photographs and evaluated improvement of pigmentation on a 4-point scale. Patient satisfaction was also rated on a scale from 0 to 10. Eleven of 14 patients in Group A had more than 50% improvement in pigmentation based on the 4-point scale, with difference in improvement between treatment and placebo groups statistically significant at $p = .027$. Patient satisfaction was also significantly better in treatment group, with $p = .003$.

In 2019, Waibel and colleagues[27] showed that NAFL resulted in better repigmentation of hypopigmented scars as compared with treatment with AFL, but superior results were achieved with AFL followed by topical bimatoprost. There was no treatment arm consisting of NAFL plus bimatoprost. Group 1 received 1550-nm nonablative, fractional erbium–doped, fiber laser treatment, Group 2 received 10,600-nm fractional ablative resurfacing, Group 3 received 10,600 nm fractional ablative resurfacing with topical bimatoprost 0.03% massaged over the treatment area for 30 to 60 seconds and then twice daily for 14 days. Group 4 received AFL followed by an epidermal harvesting system, whereby epidermal cells harvested from a nearby donor site were transferred to the AFL treatment area. Laser parameters were set to 150 to 300 micrometer depth. All patients received 3 total treatments at 4-to 6-week intervals and followed up at 6 months. Three blinded dermatologists assessed pigmentation in 80 photographs taken at baseline visit and at 6 months follow-up, presented at random. Improvement was rated on a four-point scale with Group 3 (AFL plus topical bimatoprost) scoring significantly better than the other treatment arms: 76% of patients scored more than 50% improvement with $p < .001$. All Fitzpatrick skin Types were represented. Of note, the authors hypothesized that because most of treatment Group 3 consisted of Fitzpatrick Type III, there may be a connection between darker skin Types and more robust treatment response.

Also in 2019, da Silva and colleagues[36] treated 4 patients (Fitzpatrick skin Types II–IV) with hypopigmented scars on the head and neck with a 2,940 nm CO_2FL followed immediately by 0.03% topical bimatoprost massaged into the treated area. Laser parameters were as follows: 12.5 mJ, 300 milliseconds, and 100 mtz/cm.[2] Patients returned for 3 additional treatment sessions every 2 weeks. Clinical photographs were taken on the first and four-week follow-ups, and patient satisfaction surveys were administered. Follow-up examination 4 weeks after the last treatment showed overall clinical improvement and repigmentation, with 2 patients stating that they were very satisfied with the results and 2 stating that they were satisfied. These results coincided with clinician's clinical assessment of overall improvement in pigmentation.

Discussion

Hypopigmentation within scars remains a difficult clinical problem to treat effectively. Conservative management has shown to not improve pigmentation. UV-based laser systems such as excimer laser achieve good results, but frequent touch-up visits are required indefinitely for maintenance.

Nonablative fractional laser or AFL treatment alone also results in some improvement in pigmentation likely due to the stimulation of remodeling in the dermis, but delivery of prostaglandin analogues through microscopic channels created by AFL seems to provide superior results. Ablative fractional laser followed by the application of topical agents, such as prostaglandin analogues and retinoids, have achieved long-lasting improvements in some patients. However, not all patients achieve improvement, and waning of pigmentation can occur.

Disadvantages to laser therapy include pain during the procedure, risks of infection with associated prolonged wound healing (although this is very rare), ulceration, PIH, and worsened scarring (also rare).[3,37] However, for many patients seeking return of pigmentation, these potential risks are manageable.

In future work, it may be helpful to standardize the methods used to measure repigmentation within a scar such as with colorimetry, as the results mentioned in most of the above studies rely on qualitative visual scales. Although appearance to the naked eye may be the most important outcome to the patient, more detailed information about melanocytic activity and the overall degree of repigmentation within individual cells would aid in the development of future treatments for hypopigmentation.

Additionally, comparisons in efficacy between prostaglandin analogues latanoprost, bimatoprost, and prostaglandin analogues followed by topical retinoids or calcineurin inhibitors may help to elucidate ideal treatment

combinations of topical adjuvants. Finally, the determination of success of repigmentation in different Fitzpatrick skin Types is warranted and may provide additional information on the mechanism behind repigmentation.

Conclusion

Reliable improvement of hypopigmentation in scars after laser treatment is challenging. Laser can achieve success in some cases. Ultraviolet laser can achieve modest repigmentation; however, results are short-lived and require continued re-treatment. Modest improvement in pigmentation is seen with NAFL or AFL alone, and enhanced repigmentation is demonstrated when combining fractional laser resurfacing with topical application of synthetic prostaglandin analogues and other known modulators of melanogenesis.[12]

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