54 Postinflammatory Hyperpigmentation

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Abstract

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis due to overproduction of melanin from cutaneous inflammation or injury. PIH can occur in all skin types and can be very difficult to treat. Treatment can be medical or procedural. Medical therapies include topical depigmenting agents such as hydroquinone, azelaic acid, kojic acid, and licorice extract, as well as topical retinoids, vitamin C, and sunscreens. Procedures that may be used to treat PIH include chemical peels, blue light photodynamic therapy (PDT), and various lasers including but not limited to the Q-switched ruby laser, the Q-switched Nd:YAG laser, and the fractional laser. The data available in the literature is limited to scarce case reports and case series. More studies need to be carried out to determine the overall effectiveness of each of the laser treatments described above.

Keywords

Postinflammatory · Hyperpigmentation · PIH Procedural therapy · Lasers · Q-switched ruby laser · Q-switched Nd:YAG laser

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Epidemiology

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis due to the overproduction of melanin resulting from cutaneous inflammation or injury (level 5) [1]. Inflammatory mediators including leukotrienes (LT-C4 and LT-D4), prostaglandins (PG-E2 and PG-D2), thromboxane-2, interleukin (IL)-1 and IL-6, tumor necrosis factor (TNF)-alpha, epidermal growth factor, reactive oxygen species, and nitric oxide have been shown to stimulate melanocyte activity (level 1a, 5, 5) [2–5]. Ongoing inflammation and additional ultraviolet light exposure can worsen PIH (level 5) [6].

PIH affects all age groups and can occur anywhere on the body (level 4) [7]. The affected areas are determined by the location of underlying causative dermatoses. It shows no gender predilection; however, it is more common in darker Fitzpatrick skin types. The lesions are irregularly shaped macules and patches and can vary in color from light brown to bluish gray depending on the level of deposition of pigment in the skin (level 3a) [8]. PIH can be localized in the epidermis, the dermis, or both. Epidermal PIH involves increased production of melanin and its transfer to keratinocytes; it is characterized by tan to dark brown macules or patches in the same distribution as that of the preceding inflammatory process [2]. Dermal PIH involves melanin that transgresses a damaged basement membrane,

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which is then phagocytosed by macrophages, or macrophages that transgress the basement membrane to phagocytose melanin and then regress to the dermis (level 5) [9]; the pigment appears gray-blue or gray-brown (level 5) [9, 10].

Common instigators include acne, pseudofolliculitis barbae, insect bites, atopic dermatitis, contact dermatitis, psoriasis, pityriasis rosea, lichen planus, lichenoid drug reactions, lupus erythematosus, herpes zoster, fixed drug eruptions, irritants, burns, trauma, or cosmetic procedures including laser treatments (level 2c) [2, 3, 8, 11, 12]. PIH of the epidermis resolves spontaneously in most patients within months to years without therapy [2]; however, dermal PIH is persistent and can be recalcitrant to therapy (level 3a) [2, 13].

PIH can occur in all skin types; however, there is a higher frequency and severity in people of skin of color (skin types IV, V, VI (level 3a) [14]) compared to Caucasians (level 2c, 2b) [15, 16] such as in African Americans, Hispanics/Latinos, Asians (level 2c) [17], Native Americans, Pacific Islanders, and those of Middle Eastern descent (level 3a, 2c, 1b) [2, 15–25]. Furthermore, the degree of an individual's constitutive pigmentation may indicate a higher propensity for PIH [17]. The exact incidence of PIH is unknown. There is a reported prevalence of PIH of 5.8% for children of Middle Eastern descent (level 2c) [26]. The prevalence of pigmentary disorders in the United States ranges from 9% to 19.9% for blacks [16], 0% to 1.7% for whites, 6% to 7.5% for Hispanics/Latinos, and 56.4% to 55.9% for Arab Americans [15, 16, 23, 25]. The prevalence of pigmentary disorders outside of the United States has been reported to be 0.7–15.3% for blacks [19, 21, 24], 0.1% for whites [21], 0.42% for Arabs [19], 26.8% for Middle Eastern descent [26], 1.8% for Chinese [17], 2.7% for Malay [17], 0.3–2.3% for Indian [17], and 0.5% for mixed race [17]; no data were available for Hispanics/Latinos outside the United States.

Treatment Overview

PIH can be very difficult to treat. Treatment can be medical or procedural. Medical therapies include topical depigmenting agents such as hydroquinone, azelaic acid, kojic acid, and licorice extract, as well as topical retinoids and vitamin C [8]. These agents can be used alone or in combination with other therapies and work best for epidermal PIH [6]. Additionally, photoprotection including application of a broad-spectrum sunscreen with sun protection factor (SPF) greater or equal to 30, sun avoidance, and the use of photoprotective clothing should be recommended to all patients to prevent worsening of PIH [18].

Procedures that may be used to treat PIH include chemical peels, blue light photodynamic therapy (PDT), and various lasers. Importantly, all of these procedures used to treat PIH also have the probability to worsen it if they produce excessive inflammation. Chemical peels including salicylic acid peels and glycolic acid peels have been shown to be effective for the treatment of PIH in darker skin types. In a study of five patients with skin types V and VI, Grimes demonstrated that superficial salicylic acid peels are safe and effective in the treatment of PIH (level 4) [27]. In a randomized controlled trial, Burns et al. showed that serial glycolic acid peels in addition to a topical regimen consisting of 2% hydroquinone/10% glycolic acid gel twice daily and 0.05% tretinoin cream at night was more effective in treating PIH in skin types IV, V, and VI than the topical regimen alone. Both treatment groups had improvement in PIH, but the peel group had a faster and greater improvement as well as increased lightening of the normal skin (level 1b) [28]. Blue light PDT is an established treatment for acne vulgaris. One case report of a black female with acne vulgaris treated with blue light PDT described an improvement of not only her acne lesions but also her PIH, thereby proposing blue light PDT as an effective treatment for PIH (level 4) [29].

Lasers are another therapeutic modality used in the treatment of PIH. They need to be used with caution as they can exacerbate PIH inadvertently. It is important to note that efficacy data for using lasers to treat PIH are limited to case reports and small case series. The lasers used to treat PIH that have been described in the literature include the Q-switched ruby laser (QSRL), the Q-switched Nd:YAG laser, and the fractional laser (both erbium:YAG and CO_2 lasers).

The Q-switched ruby laser has been shown to have variable results. Taylor et al. showed no improvement in eight patients with either melasma or PIH treated with the Q-switched ruby laser with the following settings: 694 nm wavelength, 40 ns pulse duration, and fluences of 15–7.5 J/cm^2 (level 4) [30]. However, Tafazzoli et al. reported an improvement of 75–100% in 58% of patients with post-sclerotherapy hyperpigmentation who were treated with the Q-switched ruby laser (level 4) [31].

The Q-switched Nd:YAG laser has been demonstrated to be an effective treatment for PIH. Cho et al. reported a series of three patients with PIH who were successfully treated with five sessions of Q-switched Nd:YAG laser at fluences of 1.9–2.6 J/cm^2 (level 4) [32]. These treatments required minimal downtime, and there was no posttreatment bleeding or crusting. The authors postulated that the longer 1064 nm wavelength leads to less risk of developing PIH after the laser treatment due to its depth of penetration [32]. Another study that evaluated 20 patients with acne and PIH showed a greater than 50% statistically significant improvement in PIH after treatment with the 1064 nm Q-switched Nd:YAG laser (level 1b) [33]. Further studies are necessary to determine the efficacy and safety of the Q-switched ND:YAG laser for the treatment of PIH.

Fractional lasers have had mixed results in treating PIH. Katz et al. described a case of one patient with post-traumatic hyperpigmentation who was successfully treated with the 1550 nm erbium-doped Fraxel laser. The patient achieved near-complete resolution with three treatment sessions using a density of 880–1100 MTZ/cm^2 [7]. Furthermore, the 1927 nm fractionated thulium laser was described to achieve near-complete resolution of post-inflammatory hyperpigmentation caused by cupping in a 26-year-old female (level 4) [34]. Rokhsar et al. reported a case of one patient with PIH induced by CO_2 nonablative laser resurfacing who was treated with the 1550 nm Fraxel laser at densities of 2000–3000 MTZ/cm^2. They described an improvement of 50–75% after five sessions over a 2-month period with no adverse events (level 4) [35]. Another case depicted successful treatment with complete resolution of refractory PIH with two sessions, each 1 month apart, of fractional CO_2 laser in a 24-year-old female with skin type III (level 4) [36]. However, Kroon et al. reported that fractional laser was not effective for PIH as evidenced by a series of six patients, who each had a total of five treatments (level 4) [37].

Effectiveness of Treatments

The data available in the literature is limited to scarce case reports and case series. More studies need to be carried out to determine the overall effectiveness of each of the laser treatments described above as well as whether or not the effectiveness varies based on demographics such as age, gender, and ethnicity. It is unknown whether the effectiveness has changed over time and how long the results will last. Longitudinal studies have yet to be performed. The degree of improvement reported ranges from 50% to 100% in the case series and case reports mentioned above.

Comparative Effectiveness of Common Treatments

There is a paucity of data comparing the effectiveness of one treatment modality against another. One study evaluated the treatment of pigmented lesions with the Q-switched ruby laser and the frequency-doubled Q-switched Nd:YAG laser. The authors measured clinical lightening of the lesion 1 month after a single treatment. At least 30% of lightening was achieved in all 20 patients with either the Q-switched ruby laser or the Q-switched Nd:YAG laser. The Q-switched ruby laser had a slightly better outcome than the Q-switched Nd:YAG laser. Neither treatment modality caused side effects of scarring or textural change of the skin. Patients reported more pain during the treatment with the Q-switched ruby laser; however, they reported more posttreatment discomfort with the Q-switched Nd:YAG laser (level 4) [38].

To our knowledge, there were no other studies in the literature examining relative effectiveness, combination treatments, or prognosis. There is

likely some variability of outcome based on patient demographics, as well as condition-specific factors such as severity, type, or anatomic location. However, more studies need to be carried out to evaluate whether or not these factors will play a role in the effectiveness of treatment.

Most treatment paradigms begin with hydroquinone, photoprotection, and avoidance of the initial inflammatory process if possible. This is commonly done, although there is a lack of clinical trials demonstrating efficacy. Chemical peels are most commonly added at this point with salicylic acid, which is particularly useful for skin types IV–VI in a setting of inflammatory acne as a causative factor. Much less common is the use of lasers due to mixed results in a small number of case series studies, higher cost compared to medical therapies and chemical peels, and limited availability of devices in practice.

Preoperative Evaluation and Patient Selection

The preoperative evaluation is very important in selecting the right treatment for an individual patient. One such tool that can aid in determining what kind of PIH the patient has is the Wood's lamp. It can be a useful tool to differentiate between primary epidermal melanosis and primary dermal melanosis. This is most helpful in patients with skin types I–IV. Primary epidermal melanosis under Wood's lamp appears as well-circumscribed pigmentation with accentuated borders, whereas primary dermal melanosis is poorly circumscribed and is not accentuated under Wood's lamp illumination [13]. Based on the location of the pigment, the treatment plan can be tailored for optimal results.

PIH tends to improve slowly over time. Therefore, treatment is not necessary for all patients. Medical therapy and/or procedural therapy can be limited to patients who desire accelerated resolution of hyperpigmentation. Procedural therapy can also be considered for those patients whose PIH is refractory to medical treatments.

There are many factors that can influence the outcome of treatment. The location of the increased pigment within the skin is one example. Medical therapies work better for epidermal pigment than they do for dermal pigment. They reduce the production or distribution of epidermal pigment. Patients with increased melanin within the dermal macrophages are less likely to respond well to medical treatment [6]. Laser treatments can be used for either epidermal or dermal hyperpigmentation.

Impact of Patient Preference

A patient's propensity to choose to proceed with any given procedure depends on many factors including cost, discomfort during and after the procedure, adverse events, number of treatments required, and likelihood of improvement or resolution of their condition. The procedures described above vary considerably with regard to postoperative care and expected side effects. Superficial chemical peels require minimal immediate postoperative care. A thin coat of petroleum jelly or Aquaphor ointment is applied after most peels. If the patient has a more robust reaction, a topical steroid can be used. Additionally, in patients with skin type IV or greater, a topical steroid may reduce the risk of developing PIH from the procedure itself. Patients can expect their newly peeled skin to develop mild-to-moderate erythema in the first few days and superficial desquamation in the subsequent few days. The patient should be instructed to cleanse the peeled skin twice daily with gentle soap and water and to resume his or her normal skincare routine once the skin is back to baseline. This can take anywhere from 1 day to 1 week depending on the depth of the peel. If the patient has a history of facial herpes simplex outbreaks, it is best to prescribe prophylactic antiviral therapy. Photoprotection is of utmost importance in the post-procedural period, and broad-spectrum sunscreen with SPF $\geq$30 should be applied as soon as the skin can tolerate it [39].

Laser therapy requires immediate postoperative cooling with ice packs. This can reduce post-procedure perifollicular edema, which typically lasts for up to 48 h, and erythema, which can

persist up to 1 week, as well as reduce postoperative discomfort. If erythema persists beyond 10 days, a low- to mid-potency topical steroid can be applied. Some patients can develop an urticarial reaction, which is best managed with oral antihistamines. Crusting can develop and last from 7 to 10 days. This can be treated with twice-daily application of petroleum jelly or Aquaphor ointment. Patients should avoid picking or scratching the area. Similar to superficial peels, photoprotection and the use of sunscreen is highly recommended after the procedure. Analgesics are typically not required as long as the appropriate cooling measures are in place before, during, and after the laser treatment [39].

The fractional ablative lasers have a slightly longer downtime as compared to other lasers and superficial chemical peels and require more extensive wound care in the post-procedural period. The fractional Er:YAG resurfacing laser can cause erythema and swelling that lasts for an average of 3 days, whereas the fractional CO_2 laser has a downtime period of about 1 week on average and includes hemorrhagic crusting, swelling, and erythema. Wound care for proper re-epithelialization includes an occlusive dressing placed on the treated area for the first few days. The patient should cleanse the affected area daily. Alternatively, lukewarm water soaks can be performed to minimize crusting. As in the other procedures, liberal use of emollients such as petroleum jelly is necessary. It is important to note that erythema can persist even after re-epithelialization and the patient should be advised accordingly [39].

Given the variable efficacy for all of the procedures and medical treatments described above, patients select a treatment plan based on the combined variables of personal distress with their situation and available time and financial resources for the treatments.

Typical Treatment Plan

A 47-year-old female with skin type III presents to the clinic with facial PIH secondary to acne vulgaris. Her acne is under good control and her face is clear with the exception of the PIH that remains. She is interested in pursuing treatment for PIH. The gold standard for the treatment of this patient is topical hydroquinone. The data are limited for PIH, but hydroquinone has been extensively studied in patients with melasma. Second-line treatment options include topical retinoids, Tri-Luma (compounded topical retinoid, topical steroid, and hydroquinone), azelaic acid, and superficial chemical peels. There are insufficient data to determine their relative efficacy and how they compare to hydroquinone. The efficacy data of peels was described above; salicylic acid peel would be the next step of treatment for this patient.

For refractory PIH, lasers should be considered. Anesthesia is typically not required. Most patients describe the discomfort as being analogous to a rubber band snapping the skin surface. If a patient is particularly sensitive, a topical lidocaine 5% cream or an EMLA cream can be applied prior to treatment. Immediately after the laser treatment, the patient may experience sensations of pain or stinging. Postoperative cooling and occlusive dressings can help mitigate these symptoms. When using a Q-switched laser, the clinical endpoint is immediate skin whitening. This will typically resolve within 20–30 min. The treated area can become temporarily hyperpigmented and crusts can form. Daily application of petroleum jelly or other occlusive ointments and daily cleansing with a gentle soap and water will help promote healing of the treated area; crusts will usually fall off within 7–10 days. Photoprotection including the use of sunscreen is strongly recommended.

Novel Treatments

Although oral tranexamic acid has been reported as a successful treatment for melasma, it was not effective as prophylaxis for laser-induced PIH. The study included 32 patients who underwent QSRL treatment of lentigines, and all patients were divided into two groups: one that received oral tranexamic acid 750 mg daily and one that did not. The PIH appeared on average

about 4 weeks after the laser treatment in both groups. There was no difference observed among the two groups showing that oral tranexamic acid did not prevent induction of PIH (level 1b) [40]. Although the results of this study did not support the use of oral tranexamic acid in the treatment of PIH, it is important to appreciate this innovative approach by using oral therapies in expanding out-treatment armamentarium of PIH.

Safety

In general, lasers have an overall favorable safety profile when operated correctly. The most severe but rare adverse effect is retinal injury and ultimately blindness. This can be avoided with the use of the proper eye protection. The laser operator and everyone in the treatment room must wear safety goggles that are specific to the wavelength of that laser. The patient should be instructed to close his or her eyes and to wear external goggles that are not transparent. If the periocular area is being treated, metal eye shields should be inserted into the eye for protection. Other more common, less severe adverse events include blistering, bruising, dyspigmentation, and scarring. Both lasers and chemical peels may cause worsening of the PIH if an undetermined threshold of injury is reached resulting in undefined "excessive" inflammation.

Postoperative Care and Follow-Up

Often, one treatment is not sufficient to produce desirable results. Both chemical peels and laser treatments are performed as often as every 4–6 weeks, but this is an arbitrary timeframe. It is difficult to predict how many treatments an individual patient will need given the lack of evidence available in the literature. One important factor to consider when determining a treatment schedule is skin type. Patients with darker skin types should have longer intervals between treatments to help minimize adverse events. Some patients have been reported to have complete resolution of their PIH with the treatments described above. Others showed significant improvement but were unable to achieve complete clearance of their PIH.

Observations and Recommendations

Evidence-based summary: Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Findings	GRADE score: quality of evidence
Procedural therapy can be considered for those patients whose PIH is refractory to medical treatments	C
All of the procedures used to treat PIH, including chemical peels, blue light photodynamic therapy (PDT), and various lasers, have the capacity to worsen PIH if they produce excessive inflammation	C
Chemical peels including salicylic acid peels and glycolic acid peels have been shown to be effective for the treatment of PIH in darker skin types	B
The Q-switched ruby laser has been shown to have variable results in the treatment of PIH	C
The Q-switched Nd:YAG laser has been demonstrated to be an effective treatment for PIH	C
Fractional lasers (including erbium, thulium, and CO_2) have had mixed results in treating PIH	C
Oral tranexamic acid is not recommended as prophylaxis for laser-induced PIH	B

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Self-Assessment Questions

1. Which of the following is true regarding PIH?
   (a) PIH is more common in the elderly
   (b) PIH is more common in females
   (c) PIH is more common in darker Fitzpatrick skin types
   (d) PIH is localized to the epidermis only
   (e) PIH is more common on the forearms
2. All of the following have been used to treat PIH except:
   (a) Topical depigmenting agents such as hydroquinone
   (b) Red light photodynamic therapy
   (c) Chemical peels
   (d) Q-switched Nd:YAG laser
   (e) Fractional CO_2 laser
3. Which of the following is false?
   (a) Medical therapies work better for dermal pigment than they do for epidermal pigment
   (b) PIH tends to improve slowly over time
   (c) Laser treatments can be used for either epidermal or dermal hyperpigmentation
   (d) Epidermal melanosis under Wood's lamp appears as well-circumscribed pigmentation with accentuated borders
   (e) Dermal melanosis is poorly circumscribed and is not accentuated under Wood's lamp illumination
4. All of the following can be observed in the postoperative period after a laser treatment for PIH except
   (a) Perifollicular edema
   (b) Perifollicular erythema
   (c) Urticarial reaction
   (d) Crusting
   (e) All are correct
5. Which of the following is the most severe albeit rare adverse effect of laser therapy?
   (a) Blistering
   (b) Bruising
   (c) Dyspigmentation
   (d) Retinal injury
   (e) Scarring

Correct Answers

1. c: PIH affects all age groups. It shows no gender predilection. PIH can be localized in the epidermis, the dermis, or both. It can occur anywhere on the body. The affected areas are determined by the location of underlying causative dermatoses.
2. b: All of the above have been used in the treatment of PIH except B. Blue (not red) light PDT is another effective treatment for PIH.
3. a: All of the above statements are correct except A. Medical therapies work better for epidermal pigment than they do for dermal pigment. They reduce the production or distribution of epidermal pigment. Patients with increased melanin within the dermal macrophages are less likely to respond well to medical treatment.
4. e: All of the above can be seen in the postoperative period after a laser treatment.
5. d: All of the answer choices listed are possible adverse effects of laser therapy. However, answer D, retinal injury, is the most severe adverse effect as it can lead to blindness. This is a very rare adverse effect but a very important one that the clinician must be aware of.