EFFECTS OF TOPICAL CORTICOSTEROIDS, TOPICAL CORTICOSTEROIDS UNDER OCCLUSION, AND TOPICAL BRIMONIDINE ON THE PREVENTION OF POSTINFLAMMATORY HYPERPIGMENTATION AFTER Q-SWITCHED 532-NM ND:YAG LASER TREATMENT OF SOLAR LENTIGINES

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PAKAGAMON TUMSUTTI

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EFFECTS OF TOPICAL CORTICOSTEROIDS, TOPICAL CORTICOSTEROIDS UNDER OCCLUSION, AND TOPICAL BRIMONIDINE ON THE PREVENTION OF POSTINFLAMMATORY HYPERPIGMENTATION AFTER Q-SWITCHED 532-NM ND:YAG LASER TREATMENT OF SOLAR LENTIGINES

BY

PAKAGAMON TUMSUTTI

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Title	EFFECTS OF TOPICAL CORTICOSTEROIDS, TOPICAL CORTICOSTEROIDS UNDER OCCLUSION, AND TOPICAL BRIMONIDINE ON THE PREVENTION OF POSTINFLAMMATORY HYPERPIGMENTATION AFTER Q-SWITCHED 532-NM ND:YAG LASER TREATMENT OF SOLAR LENTIGINES
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Q-switched (QS) Nd:YAG 532-nm laser is among the most effective treatment options for solar lentigines (SLs). However, a high incidence of post-inflammatory hyperpigmentation (PIH) was reported. The available evidence on PIH prophylaxis was currently sparse and controversial. Therefore, we aimed to determine the efficacy of multiple prophylactic treatments for PIH; including topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine; in reducing the incidence of PIH following laser treatment of SLs. Thirty-eight subjects with at least eight SLs on their forearms were recruited to receive QS Nd:YAG 532-nm laser treatment. The forearms were divided into four areas: left upper, left lower, right upper, and right lower forearms. The two most prominent lesions in each area were randomly allocated to receive topical clobetasol, topical clobetasol under occlusion, topical brimonidine, or petrolatum jelly (control). The occurrence and intensity of PIH, degree of erythema, and improvement of lesions were evaluated in weeks two, four, eight, and twelve. There was no significant differences detected between the groups regarding the occurrence and intensity of PIH, and the improvement of lesions. However, posttreatment erythema was significantly lower in the lesions that received topical clobetasol and topical clobetasol under occlusion, compared to the control. Additionally, patient satisfaction was significantly greater in the topical clobetasol and topical clobetasol under occlusion groups. In conclusion, topical clobetasol, topical clobetasol under occlusion and topical brimonidine were not found to be effective in reducing PIH after laser treatment of SLs. This could be due to the ongoing inflammatory process under the skin, as well as the presence of dermal melanophages. However, topical clobetasol and topical clobetasol under occlusion may be applied in order to improve patient satisfaction after laser treatment.

Keyword : PIH prophylaxis, Post-inflammatory hyperpigmentation, Solar lentigines, Topical clobetasol, Topical corticosteroids, Topical brimonidine

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CHAPTER 1
INTRODUCTION

Background and Rationale

Solar lentigines are common benign epidermal pigmentary lesions that arise in association with chronic sun exposure. They are characterized by small, well-defined, light to dark brown macules of various sizes that usually develop on sun-exposed skin and tend to increase in size and number with age[2]. In caucasians, the incidence of solar lentigines is more than 90% in people older than 50 years of age[3]. The lesions are also common in Asians, despite better photoprotection of their skin due to high melanin content in the epidermis[4, 5].

There are several therapeutic methods for removing solar lentigines including cryotherapy, intense pulsed light, laser therapy, and chemical peels[2]. Quality-switched (QS) lasers, particularly Q-switched Nd:YAG 532 nm laser, are among the most well-known and most effective treatment options. They operate on the principle of selective photothermolysis, a technique used to selectively target the melanosomes without damaging adjacent tissue[6]. However, high incidence of post-inflammatory hyperpigmentation (PIH) has been reported in previous studies ranging from 8.47-47%, especially in people with darker skin types[4, 6-11]. Although PIH is a benign condition and usually temporary, it can be a major cosmetic concern in many patients[5].

PIH results from an increase in melanin production or an abnormal distribution of melanin to surrounding keratinocytes after skin damage or inflammation. Although the precise mechanism has not been fully explored, the increase in melanocyte activity is thought to be stimulated by reactive oxygen species that are generated in the process of inflammation, as well as inflammatory mediators such as prostanoids, cytokines, and chemokines[12]. The melanocyte-stimulating properties of these mediators have been demonstrated in multiple studies[13, 14]. In the dermis, PIH occurs as a result of damage to basal keratinocytes, which leads to a release of melanin to be phagocytosed by

melanophage in the papillary dermis and produces blue-gray discoloration on the affected skin[5, 15, 16].

In clinical practice, various strategies have been used in an attempt to reduce the occurrence of PIH after laser therapy[5]. The prevention of PIH can be categorized into pretreatment and posttreatment prophylaxis. Regarding pretreatment strategies, the published studies include the use of glycolic acid, retinoids, hydroquinone, and brimonidine, while the methods for preventing PIH after treatment include the use of sunscreen, topical corticosteroids, and tranexamic acid[17].

Topical corticosteroids, despite a small number of supporting evidence, have been used widely by many physicians in clinical practice to reduce the incidence of PIH after laser therapy. Occasionally, it is applied under occlusion in some conditions to enhance absorption[18]. Topical corticosteroids can prevent PIH through the inhibition of phospholipase A2 and suppressing the release of platelet activating factors and arachidonic acid from the cell membrane; consequently, the release of inflammatory mediators, including leukotrienes and prostaglandins, is interrupted. They further lead to the inhibition of melanogenesis[14]. Cheyasak et al. studied the efficacy of topical clobetasol on the occurrence of PIH after ablative fractional CO2 resurfacing in Asians. The incidence of PIH was significantly lower on the side of the face treated with topical clobetasol and petrolatum, compared with the side treated with petrolatum alone[19]. However, current evidence is limited and further study is needed to determine the optimal duration of use for PIH prevention[5, 20].

To enhance the efficacy of topical corticosteroids, occlusive dressings have been used in clinical practice. An in vivo study has shown a tenfold increase in efficacy of topical corticosteroids when applied under occlusion on the forearm for 96 hours[21]. Unlike the abundant publications investigating the effects of topical steroids under occlusion on psoriatic lesions, there is currently lack of evidence of PIH prophylaxis by this method. Considering the ability to enhance therapeutic effects of topical steroids with occlusive dressings, they may also have potential benefits in the use of PIH prevention[5].

Topical brimonidine gel, a selective α-2 adrenergic agonist that causes vasoconstrictive effect on dermal blood vessels, has been approved as a treatment for facial rosacea[22]. A few case reports have shown that topical brimonidine gel 0.33% may have a potential effect in reducing posttreatment erythema and PIH after laser therapy[23-25]. The mechanisms by which topical brimonidine reduces PIH after laser treatment is not clearly understood. Previous studies in patients with solar lentigo and melasma suggested that an increased blood flow and vascularity may be associated with pigmentation[26, 27]. Therefore, reducing blood flow through the vasoconstrictive effect of topical brimonidine maybe another preventive measure for PIH[5].

At the present time, unlike the large number of literatures focusing on the treatment of PIH, the available evidence of PIH prophylaxis is currently sparse and controversial. Therefore, the aim of this study is to determine the efficacy of multiple prophylactic strategies, including the use of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine, in reducing the incidence of PIH following a Q-switched laser treatment of solar lentigines[5].

Research Questions

Primary Research Question

In patients with solar lentigines who underwent laser treatment, what are the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing the incidence of PIH, compared to the control?

Secondary Research Questions

1. In patients with solar lentigines who underwent laser treatment, what are the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing the intensity of PIH, compared to the control?

2. In patients with solar lentigines who underwent laser treatment, what are the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing posttreatment erythema, compared to the control?

3. In patients with solar lentigines who underwent laser treatment, what are the effects of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine on the improvement of lesions, compared to the control?

4. In patients with solar lentigines who underwent laser treatment, how satisfied are the patients with the results after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis, compared to the control?

5. In patients with solar lentigines who underwent laser treatment, what are the adverse effects and duration of wound healing process after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis, compared to the control?

Research Objectives

Primary Objective

To determine the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing the incidence of PIH; which will be assessed by dermatologists from digital photographs; in patients with solar lentigines who underwent laser treatment, compared to the control.

Secondary Objectives

1. To determine the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing the intensity of PIH; which will be assessed subjectively using a 5-point grading scale, and objectively by measuring melanin index using a Mexameter® MX18; in patients with solar lentigines who underwent laser treatment, compared to the control.

2. To determine the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing posttreatment erythema; which will be assessed subjectively using a 5-point grading scale, and objectively by measuring erythema index using a Mexameter® MX18; in patients with solar lentigines who underwent laser treatment, compared to the control.

3. To determine the effects of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine on the improvement of lesions; which will be assessed subjectively using a 5-point grading scale; in patients with solar lentigines who underwent laser treatment, compared to the control.

4. To determine the satisfaction of the patients after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis in patients with solar lentigines who underwent laser treatment, compared to the control.

5. To determine the adverse effects and duration of wound healing process after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis in patients with solar lentigines who underwent laser treatment, compared to the control.

Research Hypotheses

Primary Hypothesis

In patients with solar lentigines who underwent laser treatment, the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing the incidence of PIH are better than efficacy of the control.

Secondary Hypotheses

1. In patients with solar lentigines who underwent laser treatment, the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing the intensity of PIH are better than efficacy of the control.

2. In patients with solar lentigines who underwent laser treatment, the efficacy of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in reducing posttreatment erythema are better than efficacy of the control.

3. In patients with solar lentigines who underwent laser treatment, the improvement if lesions after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis are different from the improvement of lesions after using the control intervention.

4. In patients with solar lentigines who underwent laser treatment, the satisfaction of the patients after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis are higher than the satisfaction of the patients after using the control intervention.

5. In patients with solar lentigines who underwent laser treatment, the adverse effects and duration of wound healing after using topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine for PIH prophylaxis are different from the adverse effects and duration of wound healing after using the control intervention.

Scope of the Research

This study focused on the comparison between the efficacy of topical corticosteroids, topical corticosteroids under occlusion, topical brimonidine, and the control, in reducing the incidence of PIH, intensity of PIH and posttreatment erythema in patients with at least 8 solar lentigines on the forearms who underwent single session of 532-nm Q-switched Nd:YAG laser treatment at Srinakharinwirot university skin center. The lesions should be located on 4 different areas of the forearms; including left upper forearm, left lower forearm, right upper forearm, and right lower forearm; and there should be at least 2 lesions in each area. The lesions in each area were randomly allocated to receive different methods of PIH prophylaxis and lesions in one area received petrolatum jelly as a control intervention. The duration of this study were 12 weeks[5].

The incidence of PIH was determined by dermatologists using digital photographs taken at baseline, and 2, 4, 8 and 12 weeks after laser treatment. PIH was defined as an increase in pigmentation, at the area where the lesions were previously located, after the crust had fallen off following the laser treatment. The degree of PIH, degree of erythema, and improvement of lesions were subjectively evaluated using 5-point grading scales. The melanin index and erythema index were assessed using a Mexameter® MX18 (Courage-Khazaka electronic GmbH, Cologne, Germany). The measurements were performed at baseline, and 2, 4, 8 and 12 weeks after laser treatment.

In addition, the duration of wound healing was recorded in the patient's logbook and the adverse effects were also recorded at each visit. The patients evaluated their satisfaction score at the end of the study using a 5-point grading scale[5].

Research Design

An experimental, prospective, randomized, single-blinded, controlled, intra-individual, comparative study

Expected Benefits

1. The efficacy and safety of topical corticosteroids, topical corticosteroids under occlusion, and topical brimonidine in preventing PIH and posttreatment erythema in patients with solar lentigines who underwent laser treatment will be determined.

2. The interventions that are found to be significantly effective will be used in clinical practice to lower the risk of PIH after laser therapy of solar lentigines.

3. The patient satisfaction after the laser treatment of solar lentigines may be increased.

4. The results may contribute to an evidence-based guideline for PIH prophylaxis after laser treatment and other dermatologic procedures.

Definition of Terms

1. Post-inflammatory hyperpigmentation is defined as an acquired hypermelanotic change that occurs after skin injury or inflammation

2. Posttreatment erythema is defined as redness of the skin due to increased blood flow in superficial blood vessels that occurs after dermatologic procedures

3. PIH prophylaxis is defined as an action taken to prevent occurrence of hyperpigmentation after dermatologic procedures

Conceptual Framework

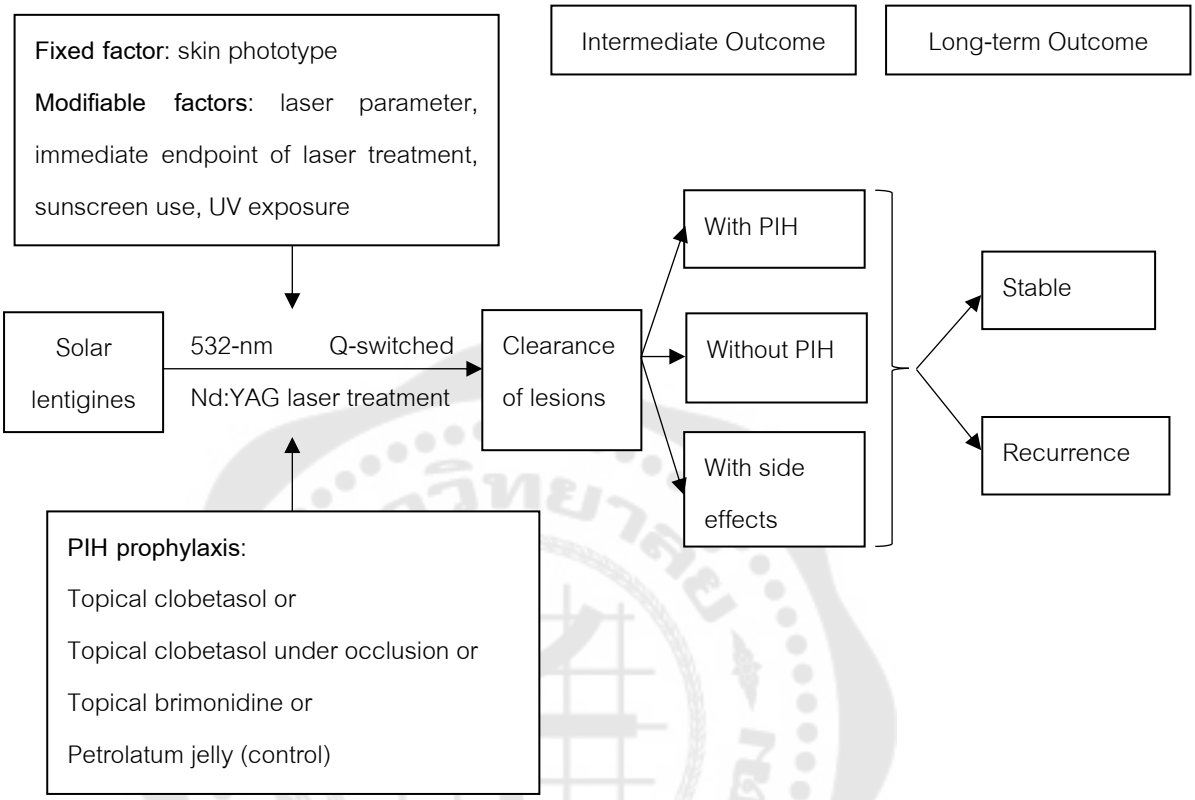


Figure 1 Conceptual framework

CHAPTER 2
LITERATURE REVIEW

In this chapter, the researcher has reviewed related publications and summarized the information as follows:

1. Solar lentigines
2. Treatment of solar lentigines
3. Post-inflammatory hyperpigmentation (PIH)
4. PIH after 532-nm Q-switched Nd:YAG treatment of solar lentigines
5. PIH prophylaxis

Solar Lentigines

Introduction

Solar lentigines (actinic lentigo, lentigo senilis, senile lentigines, liver spots) are common benign hyperpigmented lesions that usually affect Caucasians and individual with fair skin. The incidence of the condition increases with age. Chronic, intermittent sun exposure is thought to play a significant role in the appearance of the lesions. Histologically, they can be categorized as early seborrheic keratoses[1]. Despite the fact that they are benign, many patients can be concerned due to their appearance on highly visible areas of the skin[2].

Epidemiology

The incidence of solar lentigines increases with age. They affect more than 90% of the Caucasians aged older than 60 years[3]. The lesions are also common in Asians, despite better photoprotection of their skin as a result of higher melanin content in the epidermis[4]. In younger individuals, solar lentigines commonly appear following a history of acute sunburn[1].

Pathogenesis

One of the most important associated factors of the occurrence of solar lentigines is cumulative intermittent ultraviolet (UV) exposure, which results in an increase in melanin production[4]. The induction of skin pigmentation by UV irradiation, particularly

UVB, is regulated by cellular interactions between melanocytes and surrounding cells, including epidermal keratinocytes and dermal fibroblasts. Keratinocytes are known to produce various inflammatory cytokines and growth factors that influence the growth and activity of melanocytes in response to UV exposure. Interleukin-1-α (IL-1- α), one of the inflammatory mediators produced by keratinocytes, stimulates dermal fibroblasts to produce keratinocyte growth factor (KGF), which in turn promotes the proliferation of keratinocytes and accelerates melanosome transfer, leading to excessive melanin accumulation in keratinocytes[28, 29]. A role of photo-induced fibroblasts has been suggested as an important factor in the development of UV-associated pigmented lesions such as solar lentigines or melasma[30, 31]. Long-term UV exposure induces the secretion of vascular endothelial growth factor (VEGF) from keratinocytes, which contributes to angiogenesis and vascular permeability[32]. Considering previous evidence reporting that endothelial cells can induce melanin synthesis, it is likely that microvasculature plays a role in the development of pigmentary disorders induced by UV exposure[33]. Moreover, it was reported that UV exposure promotes the recruitment of macrophages to the skin, which also plays a significant role in UV-induced melanin production. VEGF-expressing macrophages are thought to be associated with the increased vasculatures in solar lentigines[34].

Clinical Presentations

Solar lentigines are one of the signs of photo-aged skin. They are characterized clinically by well-defined, irregular, round to oval, brownish macules of various sizes ranging from a few millimeters to more than one centimeter in diameter. They usually develop on chronic sun-exposed areas such as face, neck, hands, and dorsal forearms and tend to increase in size and number with age[2]. In younger individuals, the lesions are commonly seen on sun-exposed areas such as face and shoulders after a history of acute sunburn[35].

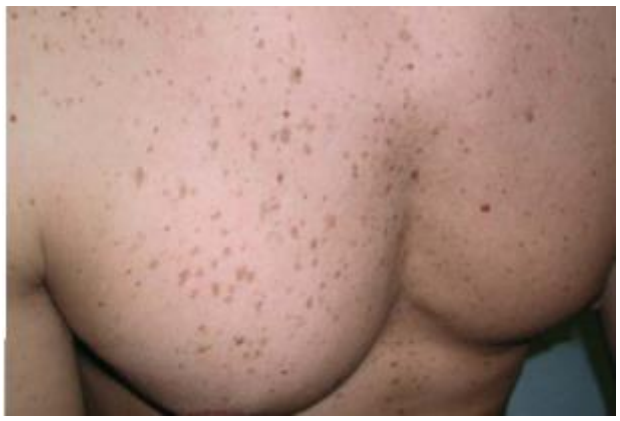


Figure 2 Solar lentigines in younger patients[35]

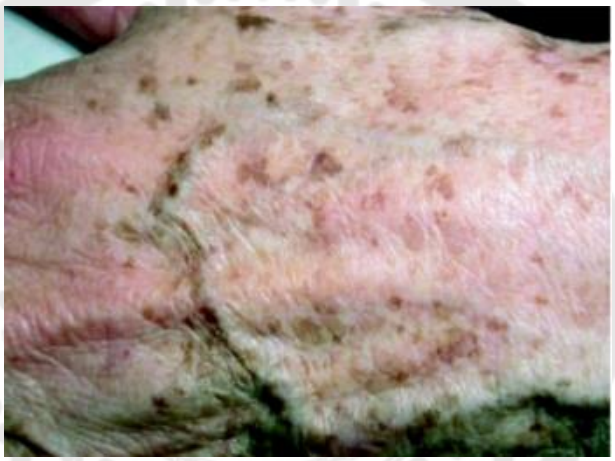


Figure 3 Solar lentigines after chronic sun exposure[1]

Dermoscopic Features

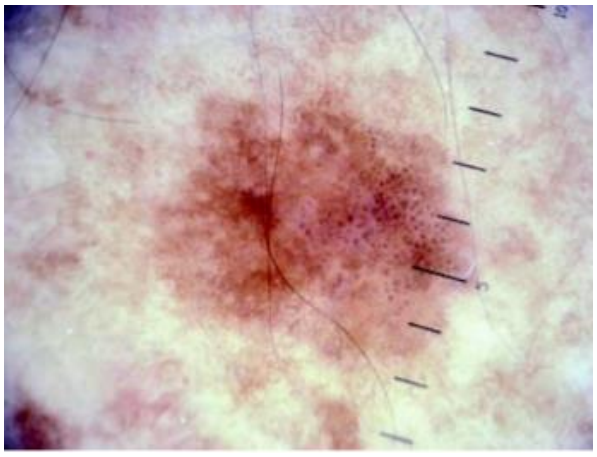


Figure 4 Solar lentigo (dermoscopic image)[1]

On dermoscopy, solar lentigines appear homogeneous and uniform in color with a moth-eaten or jelly-like edge. Dermoscopic features of solar lentigines on the face usually appear as diffuse pigmentation with round hypopigmented follicular openings called pseudo-network, similar to seborrheic keratoses[1]. Lesions characterized by irregular brown dots or globules on brownish background or annular-granular pattern should be carefully monitored for the development of lentigo maligna[36].

Histopathology

On histopathology, an increase in melanocytes can be seen in a linear pattern at dermo-epidermal junction without a characteristic of cellular atypia. Solar elastosis is often seen as an associated finding. The epidermis shows a formation of elongated bud-like or club-shaped rete ridges expanding into papillary dermis. There may be minor hyperkeratosis in the stratum corneum[1].

Diagnosis

Solar lentigines can be diagnosed clinically. To improve the accuracy of diagnosis, dermoscopy can be used to visualize the structure of the lesions[37].

Differential Diagnosis

Lentigo maligna and solar lentigines on the face may have similar characteristics. The homogeneous coloration and lack of ABCDE signs of malignancy can make it difficult to distinguish between the two conditions. Dermoscopic examination can be beneficial in the evaluation of these lesions[1].

Simple lentigines, resembling solar lentigines, commonly appear as light to dark brown macules in round to oval shape. They are approximately 3-5 mm in diameter and may coalesce. The lesions can be located on any area of the skin and muco-cutaneous junction, whereas solar lentigines are mostly located on sun-exposed skin[1].

Freckles or ephelides can occasionally be mistaken as lentigines. They are small, well-defined, light brown macules that are located on sun-exposed areas of the body such as face, forearms, and dorsum of hands. They are common in individuals with fair skin and usually develop in the childhood[38].

Another differential diagnosis for solar lentigines are seborrheic keratoses. They are common in the elderly and characterized as warty or waxy papules or plaques

that are variable in color and can appear as a solitary or multiple lesions. In contrast to solar lentigines, their development are independent of sun exposure and is likely due to focal impairment of epidermal homeostasis, which leads to proliferation of melanocytes and keratinocytes[39]. However, early lesions of seborrheic keratoses can resemble the lesions of solar lentigines.

Prognosis

Solar lentigines are persistent if left untreated. Although benign, these lesions are aesthetically unappealing to many patients. Cryotherapy and laser treatment are usually effective in removing the lesions; however, post-inflammatory hyperpigmentation may occur following the treatment[40].

Treatment of Solar Lentigines

Treatment of solar lentigines can be categorized into 2 groups: physical therapy and topical therapy. A range of physical therapies are frequently used with high success rates, including cryotherapy, laser therapy, intense pulsed light therapy, and chemical peels. However, the risk of adverse effects and recurrence must be taken into consideration before using these methods. Topical therapy of solar lentigines includes hydroquinone (HQ), tretinoin, adapalene, a combination of mequinol and tretinoin, and epidermal growth factor (EGF). Longer duration is usually required for the topical therapy to achieve satisfying results. In addition, sunscreens are generally used to protect the skin from UV radiation[2].

Physical Therapy

1. Cryotherapy

Cryotherapy is one of the most common methods used to remove solar lentigines. A list of cryogens includes carbon dioxide, nitrous oxide, and liquid nitrogen. The agent can be applied using a cotton swab or a hand-held spray unit. At temperatures of -4°C to -7°C, cell freezing occurs which leads to melanocyte destruction[41]. One freeze-thaw cycle is generally adequate to remove solar lentigines, while multiple freeze-thaw cycles can produce deep tissue necrosis. Local pain, blistering, and local swelling are common temporary adverse effects[2]. More permanent adverse effects include post-

treatment hyperpigmentation or hypopigmentation. A recurrence rate of 55% after 6 months has been reported in previous study[42] and a clearance rate is lower when compared with laser therapy[43].

2. Laser Therapy

Melanin has broad spectrum of absorption, ranging from 351 to 1064 nm. Lasers that have been used in published reports to treat pigmented lesions, particularly solar lentigines, include 510-nm pulsed dye laser, 511-nm copper vapor laser, 520-nm or 530-nm krypton laser, 532-nm Q-switched Nd:YAG laser, 694-nm Q-switched ruby laser, 755-nm Q-switched alexandrite laser, 1064-nm Q-switched Nd:YAG laser, 10,600-nm CO_2 laser, and 488-nm to 630-nm argon laser. Continuous and quasicontinuous lasers have higher risk of developing hypopigmentation and hyperpigmentation compared to the short-pulsed lasers, especially in individuals with darker skin types[44]. With short-pulsed lasers, higher fluences can be used while maintaining better control of tissue damage.

Q-switched lasers are primarily used in the treatment of solar lentigines. They operate on the basis of selective photothermolysis which allows for the clearance of lesions while minimizing injury of the surrounding tissue. The lasers generate a sudden rise in temperatures which leads to the evaporation of pigments in the skin (photothermal reaction) and the formation of gas bubbles in the cells result in rupture of melanosomes into small fragments (photomechanical reaction)[6, 45]. A previous study using Q-switched ruby laser for removal of solar lentigines in 8 women has reported that a single session of treatment resulted in improvement of the lesions without scarring[46]. Q-switched alexandrite laser has been reported in 11 patients with solar lentigines to provide excellent responses in most patients[47].

One of the most commonly used lasers for removing solar lentigines is 532-nm Q-switched Nd:YAG laser due to its highest level and quality of evidence in treatment of solar lentigines[2]. The clearance rate of the lesions was reported to be more than 50% as demonstrated in a previous study. However, post inflammatory hyperpigmentation after treatment is not uncommon, particularly in patients with darker skin types (Fitzpatrick skin type III-IV)[6].

3. Intense Pulsed Light Therapy

Intense pulsed light (IPL) is a broad-spectrum visible light emitted from a noncoherent, filtered light source. Multiple sessions of treatment are required for a significant improvement of solar lentigines. A study in Asian population has demonstrated more than 50% improvement of solar lentigines after 3-5 sessions of IPL treatment at an interval of 2-3 weeks in 40% of the patients without any evidence of hyperpigmentation or scarring[48].

4. Dermabrasion

Dermabrasion is a process that removes superficial skin mechanically. The procedure is performed with a motor-driven rotating diamond fraise or wire brushes mounted on a handpiece. It is most commonly used for the improvement of scars, rhytides, and facial skin texture[49]. The depth of treatment can be varied, depending on the pressure applied to the skin. At the depth beyond papillary dermis, various adverse effects can occur, including bleeding spots, hyperpigmentation, and hypopigmentation[50]. It has been used for removing solar lentigines in a previous study. At 6 months after treatment, a recurrence rate of 55% has been demonstrated[42].

5. Chemical Peels

Chemical peeling is the use of exfoliative agents to improve multiple cutaneous conditions. The improvement of dyspigmentation has been observed in studies using glycolic acid[51], trichloroacetic acid (TCA)[52], Jessner's solution[53], and salicylic acid[54]. A combined solution of 40% TCA and 70% glycolic acid has been reported to be effective in improving irregular pigmentation of the skin in nonfacial areas[55]. A comparative study using either 30% TCA or cryotherapy with liquid nitrogen for the treatment of solar lentigines in 25 patients has shown that 71% of the patients in cryotherapy group achieved more than 50% improvement of the lesions. Meanwhile, only 47% of the patients in the TCA group achieved the same result. PIH, hypopigmentation, and skin atrophy were rarely noted in both groups[56]. A study comparing between 35% TCA and 532-nm Q-switched Nd:YAG laser for the treatment of solar lentigines in 20 patients also reported better outcome in the lesions treated with laser therapy[57].

Topical Therapy

1. Hydroquinone (HQ)

HQ is one of the most commonly used agents for the treatment of hyperpigmentation. It inhibits the tyrosinase enzyme; thus, preventing the conversion of dihydroxyphenylalanine (DOPA) to melanin. Additionally, HQ is also likely to cause reduction of pigmentation by disrupting DNA and RNA synthesis, degradation of melanosomes, and damage of melanocytes. A previous study in 20 Asians with solar lentigines using 2% HQ-cyclodextrin, a technology that promotes absorption of HQ into the skin, has demonstrated that applying HQ to the lesions once daily resulted in a significant decrease in pigmentation after 2 months of treatment[58].

2. Tretinoin

Tretinoin (RA) reduces skin pigmentation by inducing desquamation. It is also thought to inhibit tyrosinase enzyme. A randomized, controlled trial in 251 patients with photodamaged facial skin has reported an improvement in photodamaged skin and solar lentigines in 79% of the patients who received 0.05% RA, while the groups that received 0.01% RA and control reported improvement in 57% and 48% of the patients, respectively. Adverse effects, including erythema, stinging, and peeling, were usually well-tolerated[59].

A combination of 0.1-0.4% RA and 5% HQ has been used to treat solar lentigines in a study conducted in 136 patients. HQ was applied 2 times daily, followed by a combination of RA and HQ twice a day. After 8 weeks of the treatment, excellent results were observed in 95% of the patients with facial lesions, 66.7% of the patients with trunk lesions, and 50% of the patients with lesions on their upper extremities. Overall, a success in improvement of lesions was reported in 82.2% of the patients. High rates of erythema and irritations occurred due to the use of high concentration of RA[60].

3. Adapalene

Kang et al. conducted a randomized, controlled trial using 0.1% or 0.3% adapalene gel to treat 90 patients with solar lentigines or actinic keratoses. The treatment was applied once a day for 4 weeks, then twice a day for 9 months. After 9 months, the patients who received adapalene gel had significantly lighter lesions, compared to the

control group. Mild erythema, burning, dryness, peeling, and pruritus were observed in the treatment group[61].

4. Mequinol (4HA)/Tretinoin

4-Hydroxyanisole (4HA) or mequinol is a derivative of HQ family. Several studies have reported successful clinical improvement of solar lentigines after applying a combination of 2% 4HA and 4HA/0.01% RA for 16 to 24 weeks. The most common adverse effects were erythema, burning, stinging, desquamation, and pruritus[62-64].

5. Epidermal Growth Factor (EGF)

EGF enhances wound healing by promoting the resurfacing of damaged epidermis and inducing the development of granulation tissue, blood vessel formation, and wound contraction[65, 66]. It is typically used for the treatment of chronic skin ulcers such as diabetic foot ulcers[67]. EGF has been shown to have anti-inflammatory and antioxidant properties. It also has an anti-melanogenic effect by inhibiting tyrosinase enzyme activity, according to an in vitro study[66]. Kim et al. has reported that the use of EGF-containing ointment twice daily for 4 weeks as an adjunctive therapy for the treatment of facial solar lentigines with a 532-nm Q-switched Nd:YAG laser showed greater therapeutic effects with less PIH, compared with using petrolatum[68].

The Pigmentary Disorders Academy (PDA) has categorized the treatment options for solar lentigines as shown in table 1

Table 1 Level and quality of evidence for solar lentigines therapies[2]

Therapy	Quality of evidence	Level of evidence
Cryotherapy	I	A
Lasers		
Q-switched ruby	II-i	A
Alexandrite	II-i	B
532-nm Nd:YAG	I	A
CO_2	I-ii	B
Argon	I-ii	B
HGM K1 krypton	I-ii	B
Diolite 522-nm	II-i	B
Intense pulsed light (IPL)	III	B
Dermabrasion	III	D
Chemical peels		
30% Trichloroacetic acid (TCA)	II-ii	C
Topical		
3% Hydroquinone (HQ)	IV	C
0.01% tretinoin	I	C
0.05% tretinoin	I	A
2% 4HA (4-Hydroxyanisole; mequinol)	I	B
2% 4HA + 0.01% tretinoin	I	A
0.1-0.4% tretinoin + 5% HQ	II-iii	B
2% HQ/cyclodextrin	II-ii	C
0.1-0.3% adapalene	I	B
0.1% Tazarotene	I	B

The categories of level and quality of evidence are as shown in table 2 and 3, respectively, according to guidelines adopted from the US Preventive Services Task Force (USPSTF) on health care[69].

Table 2 Level of evidence[69]

A	There is good evidence to support the use of this procedure
B	There is fair evidence to support the use of this procedure
C	There is poor evidence to support the use of this procedure
D	There is fair evidence to support the rejection of the use of this procedure
E	There is good evidence to support the rejection of the use of this procedure

Table 3 Quality of evidence[69]

I	Evidence obtained from at least one properly designed, randomized controlled trial
II-i	Evidence obtained from well-designed controlled trials without randomization
II-ii	Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center or research group
II-iii	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be regarded as this type of evidence
III	Opinions of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
IV	Evidence inadequate owing to problems of methodology (e.g. sample size, or length or comprehensiveness of follow-up or conflicts in evidence)

As demonstrated in table 1, the treatment options with highest level and quality of evidence are cryotherapy, 532-nm Q-switched Nd:YAG laser, 0.05% tretinoin, and a combination of 2% 4HA and 0.01% tretinoin. In clinical practice, 532-nm Q-switched Nd:YAG laser is the most commonly used method to remove solar lentigines because of its good clearance rate and shorter duration of treatment. However, high incidence of PIH has been reported in previous studies ranging from 8.47-47%, especially in people with darker skin types[4, 6-10]. Despite the benign and temporary course of PIH, it can be a major cosmetic concern in many patients[5].

Post-Inflammatory Hyperpigmentation (PIH)

Introduction

Post-inflammatory hyperpigmentation (PIH) is a common, acquired hypermelanosis that occurs after inflammatory dermatoses, external skin injury, or dermatologic procedures. PIH is one of the most frequent complications of dermatologic procedures, including laser therapy. The condition can arise in all skin types but tends to affect patients with Fitzpatrick skin phototypes (SPTs) III to VI[12]. To minimize the incidence of PIH after procedures, several factors must be considered: primary diagnosis, location of the dermatoses, skin type of the patient, past history of PIH, device selection, and laser parameters. In regard to laser parameters; low fluences, low density, longer pulse width, adequate skin cooling, and avoiding sun exposure after treatment, are recommended in order to balance between the desired results and the risk of PIH[17]. In clinical practice, various strategies have been used to reduce the occurrence of PIH following dermatologic procedures. However, current evidence of PIH prophylaxis is sparse. Further studies are required to demonstrate the most effective and safest methods for the prevention of PIH.

Epidemiology

Patients with darker skin types, for example, African Americans, Latinos, East Indians, Pakistanis, and Southeast Asians, are at higher risk of developing PIH after laser therapy. Chua-ty et al. reported higher incidence of PIH among Asians with darker skin types in Singapore[70]. Dyschromia was also one of the most common adverse effects developed in African Americans, while it occurred infrequently in white individuals[71]. A study in Asians who had undergone treatment with fractional laser resurfacing reported 11.1 to 17.1% incidence of PIH[72].

A study in 125 female patients who had undergone laser toning using a Q-switched Nd:YAG laser has reported an incidence of PIH after treatment to be 16.8%. The most important risk factors for developing PIH were immediate endpoints of laser, α-hydroxy acid (AHA) peels, Fitzpatrick skin phototypes, and presence of acne or melasma[73].

Pathogenesis

The development of PIH is associated with several factors, including the skin type of the patients, sun-exposure before laser treatment, the damage of the dermal–epidermal junction, and the degree of inflammation at the basement membrane[5, 74].

There are two major processes which result in PIH: cutaneous epidermal inflammatory response, and pigmentary incontinence. Cutaneous epidermal inflammatory response results in the release of eicosanoids, including prostaglandins E2 and D2, leukotrienes B4, C4, D4, and E4, and thromboxane B2, which are generated from cell membranes after cutaneous inflammation. They contribute to the enlargement of melanocytes and increased proliferation of melanocyte dendrites, leading to an increase in melanin production and melanin transfer to surrounding keratinocytes[13, 14, 75]. Leukotriene C4 has been revealed to be the most potent mediator to upregulate tyrosinase enzyme activity[13, 14]. Moreover, other inflammatory cytokines and mediators such as tumor necrosis factor-α, interleukins-1α, interleukin-6, endothelin-1, basic fibroblast growth factor, stem cell factor, nitric oxide, and superoxide, also promote melanogenesis[13, 14, 76]. Meanwhile, pigmentary incontinence results from the damage of basal cell layer, which allows large amount of melanin to enter the dermis, following by phagocytosis of melanin by dermal macrophages, which later become melanophages[77].

Inflammation of the skin can result in hypo- or hyperpigmentation, or both, depending on the effects on the number or function of melanocytes. PIH usually occurred when the dermo-epidermal juction (DEJ) is affected[78]. The property of melanocytes can be varied between individuals; the patients can respond with normal, decreased, or increased melanogenesis of varying degrees after skin injury or inflammation[79]. This reaction is thought to be determined by genetics rather than the SPTs of the patients. Inflammation leads to multiple responses of melanocytes, including hyperplasia, hypertrophy, and increased function, then the melanin is transferred to the nearby keratinocytes.

The pathogenesis in the development and the variation in which patients develop postinflammatory hyperpigmentation or hypopigmentation are not well established. A previous study has suggested that each individual has different function of melanocytes and their responses to inflammation or skin injury with either hyper- or hypopigmentation depend on the patient's inherited chromatic tendency[79]. A study in Singapore has revealed that PIH tended to occur more among dark-skinned Asians, such as Malaysians and Indians, compared with Asians with lighter skin types. This indicates that the risk and intensity of PIH are associated with darker skin types, rather than race or ethnicity[70].

Clinical Manifestations

PIH usually presents as macules or patches in the areas of the skin where inflammation occurred. The depth of the excess melanin determines the characteristic of pigmentation[12]. Epidermal hypermelanosis appears as light to dark brown discoloration that may take months to years to completely resolve, while dermal hypermelanosis typically appears as blue-gray macules or patches that can be persistent if left untreated[80, 81]. Darker-skinned patients usually develop more severe PIH[12].

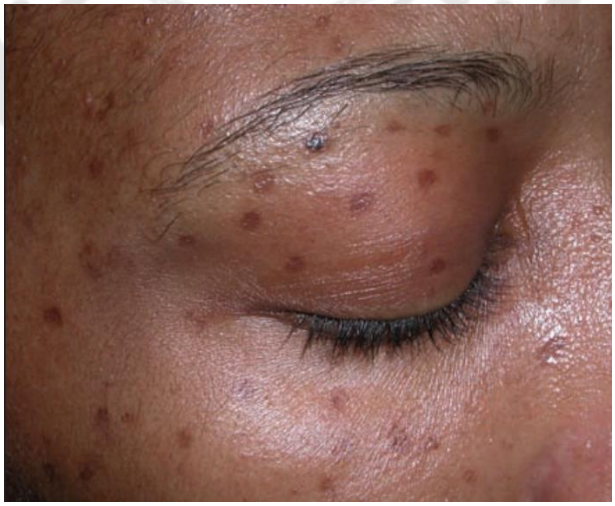


Figure 5 PIH after a dermatologic procedure[12]

Evaluation of PIH

Subjective Evaluation

1. Wood's Lamp Examination

PIH can be assessed visually by comparing the color with baseline pigmentation. One of the useful tools for diagnosis of PIH is a Wood's lamp. It emits light at UV and visible spectrum, ranging from 320 to 450 nm, with a peak wavelength at 365 nm, which is absorbed by epidermal melanin. Therefore, epidermal hypermelanosis is highlighted without affecting normal skin. However, dermal PIH is not enhanced by Wood's lamp examination due to the low penetration depth of UV radiation. Unclear results may occur in patients with SPTs V to VI because of the high concentration of melanin content in their skin[79].

2. Histopathology

In some patients, a skin biopsy may be essential for excluding other cutaneous disorders that can result in hyperpigmentation. Histopathology of PIH shows melanophages in the upper dermis and increased epidermal melanin without vacuolar alteration of basal cells. In post-inflammatory hypopigmentation, dermal melanophages also present, but with decreased epidermal melanin[78].

3. Taylor Hyperpigmentation Scale

Another tool for visual assessment of PIH is the Taylor hyperpigmentation scale, a visual scale developed as a method to evaluate skin color and monitor PIH after treatment. It consists of 15 plastic cards with different ranges of skin colors that can be used in patients with SPTs I to VI. Each plastic card contains 10 levels of hyperpigmentation[82]. However, the use of Taylor hyperpigmentation scale has not been certified[78].

Figure 6 One of the cards in Taylor hyperpigmentation scale[82]

4. Investigator's Global Assessment (IGA) Scale

A global assessment is a convenient method of measurement used to assess the severity of the disease based on an ordinal scale. At the present time, there is no standardized IGA scale. The implementations and definitions of the scale vary between studies[83].

IGA scale	Hyperpigmentation	Erythema
0	Clear of hyperpigmentation	Clear of erythema
1	Almost clear of hyperpigmentation	Almost clear of erythema
2	Mild, but noticeable hyperpigmentation	Mild, but noticeable erythema
3	Moderate hyperpigmentation (medium brown in quality)	Moderate erythema (pink in quality)
4	Severe hyperpigmentation (dark brown in quality)	Severe erythema (dark pink in quality)
5	Very severe hyperpigmentation (very dark brown, almost black in quality)	Very severe erythema (very dark pink, almost red in quality)

Figure 7 Example of IGA scale for hyperpigmentation and erythema[84]

Objective Evaluation

Objective methods for assessment of PIH provide more reliable and more reproducible outcome, compared with subjective measurement. Quantitative information can be obtained from these technologies; therefore, it allows for the more accurate analysis of pigmentation.

1. Tristimulus Colorimetry

Reflectance Tristimulus CIE Colorimetry operates based on a combination of three stimuli: red (X), green (Y), and blue (Z) light. It can be used to evaluate erythema and pigmentation in quantitative scale[85]. The device contains white LEDs arranged in a circular pattern and emit light at wavelengths of 440-670 nm to illuminate the skin. The probe is placed on the skin with uniform gentle pressure to avoid blanching effect of the skin. The primary information obtained from the measurement is converted to L*, a*, and b* values. In the L*a*b* color system, L* represents luminance ranging from 0 (black) to 100 (white), a* represents the balance between green (negative values) and red color (positive values), and b* represents the balance between blue (negative values) and yellow color (positive values)[78, 86]. For PIH, a decrease in the L*

value indicates a darkening of the pigmentation. Colorimetry has been widely used to assess skin typology[87], hyperpigmentation[88, 89], and melasma[90].

Figure 8 Colorimeter® CL 400 device[91]

Chromameter® (Minolta, Osaka, Japan) is a tristimulus colorimeter that operates based on a principle of scanning reflectance spectrophotometry. The device calculates color values according to the CIE color systems (L*a*b, or XYZ). The results are shown immediately on the screen. The disadvantages of the Chromameter include the influence of pressure on the skin, the relatively large probe head size (8-11 mm), and the less ergonomic design of the probe[86].

Dermacatch® is a reflectance colorimeter developed by the Swiss company Colorix. It contains a light source which emits the “full visible light spectrum”. The measuring area is 5.5 mm in diameter (24 mm^2). In contrast to Mexameter, the level of erythema has little to no effect on melanin values when measured by Dermacatch. It was also reported in previous study to be more sensitive and specific in measuring melanin and erythema values, compared to Mexameter[92]. However, the data obtained from Dermacatch can only be displayed on the screen and are not directly transferred to the computer[86].

2. Reflectance Spectroscopy

The scanning reflectance spectroscopy evaluates the light spectrum reflected by the skin, ranging from 400 to 700 nm. It is a technique used to evaluate the concentration of the biomolecules, including melanin, oxyhemoglobin, and deoxyhemoglobin, based on their absorption properties. Melanin and erythema indices can be measured by this method. The probe must be placed gently on the skin to avoid skin blanching. The diameter of the probe is 2.5 mm; therefore, adequate reading must be performed to analyze the difference between normal skin and the lesion[78, 86].

3. Narrow-Band Reflectance Spectroscopy

The reflectance spectrophotometers are known to be high-priced, bulky, and not suitable to be used in clinical practice. Since the results obtained from the spectrophotometry are usually analyzed in specific narrow spectra, the more convenient and less expensive methods based on narrow-band analysis were developed.

The Mexameter® MX18 (Courage-Khazaka, Electronik, Köln, Germany) is equipped with multiple light-emitting diodes (LEDs) which emit the light at 568 nm, 660 nm, and 880 nm. As the quantity of diffused and scattered light is measured, the amount of light absorbed by the skin can be evaluated. The melanin index is measured at 660-nm and 880-nm wavelengths in order to assess different absorption capacity of the melanin pigments. In regard to the erythema index, 568-nm wavelength, which corresponds to the absorption peak of hemoglobin, is used for the measurement of erythema. 660-nm wavelength is also used to avoid the interference by other components such as bilirubin[86]. The measurement can report values in a quantitative scale of 0-999 for melanin and erythema indices; thus, even the slightest alteration in color is detectable. It also provides rapid assessment; only 1 second is needed for the results to be obtained[93].

Figure 9 Mexameter® MX18[93]

DermaSpectrometer® (DSM; Cortex Technology, Hadsund Denmark), another type of narrow-band spectrophotometers, is based on two LEDs which emit green (568 nm) and red (655 nm) light. DSM can display results in L*a*b, RGB, CMYK, and XYZ color system. The erythema and melanin indices can be calculated from the inverse of reflected light intensity. The probe is equipped with a guiding light that enhances the vision of the target before reading. However, the disadvantage of the DSM is that the environmental light can interfere with the measurements[86].

Clarys et al. conducted a comparative study between the Chromameter, Mexameter, and DermaSpectrometer, in vitro and in vivo. In regard to the repeatability, all instruments were reported to perform well, except for the a* parameter of the Chromameter and the erythema index of the DermaSpectrometer[94].

4. Skin Imaging Analysis

Antera 3D (Miravex Limited, Dublin, Ireland) is a camera for image analysis of the skin. The LEDs of different wavelengths from multiple directions are used to reconstruct the image data of the skin surface in 3 dimensions. The distribution and concentration of chromophores, including melanin and hemoglobin, can be evaluated

from the data. In contrast to the regular imaging analysis, where only red, green, and blue are used, the Antera 3D uses the entire visible spectrum of light wavelengths for skin evaluation, which allows the skin properties to be analyzed more precisely. The measuring area of Antera 3D is 3,136 mm^2 (56 x 56 mm)[91].

A comparative study between Antera 3D, Mexameter and Colorimeter was conducted in 30 volunteers who were exposed to UVB light. Measurements with the three devices were done at baseline, and 2, 7 and 14 days after the intervention. In regard to the melanin value and the erythema index, Antera 3D was reported to have a better sensitivity and specificity than Mexameter. Regarding the CIE L*-a*-b* parameters, sensitivity of Antera 3D was also found to be better than Colorimeter. Additionally, for all parameters, reproducibility of the values obtained from Mexameter and Colorimeter was found to be lower than that of Antera 3D[91].

Figure 10 Antera 3D® device

VISIA® (CANFIELD Imaging Systems, Fairfield, NJ, USA) is a widely used device for skin imaging analysis. It can produce a series of high-definition images in seconds, and evaluate the overall dermatologic conditions of the patient, including spots, wrinkles, texture, pores, erythema, and porphyrin. A previous study has demonstrated that Antera 3D has better sensitivity regarding wrinkle assessment, compared with VISIA[95].

PIH After 532-nm Q-switched Nd:YAG Treatment of Solar Lentigines

A previous study has revealed that an appearance of PIH after 532-nm Q-switched Nd:YAG treatment of solar lentigines can begin at 3 to 48 weeks after treatment, with the mean onset of 4.3 weeks. It can persist for up to 2 to 24 weeks, with an average duration of 8.4 weeks[8].

Negishi et al. conducted a comparative study in 193 Asians, who had SPTs of III to V, with facial solar lentigines, using 694-nm Q-switched ruby laser or 532-nm Q-switched Nd:YAG laser. The patients were treated with one session of laser therapy and the results were evaluated at 4 weeks after the treatment. A high PIH incidence of 23.18% was reported in the group that was aggressively treated with 532-nm Q-switched Nd:YAG laser, whereas the rate of PIH in the group that received mild irradiation was 8.47%[6].

A study in 20 Korean volunteers with facial solar lentigines who were treated with 2 sessions of 535-nm Q-switched Nd:YAG laser has shown an average improvement of 72.25% in all of the patients at 4 weeks after the last session of laser therapy. PIH was observed in 20% of the patients and resolved spontaneously within 3 months[9].

A retrospective study was conducted in 40 Chinese patients with freckles or lentigines who had undergone treatment using 4 different lasers: 595-nm long pulsed dye laser (LPDL), 755-nm long pulsed alexandrite laser, 532-nm Q-switched Nd:YAG laser, and 532-nm long pulsed potassium-titanyl-phosphate (KTP) laser. Significant improvement of the lesions was found after treatment with all modalities, except for the long-pulsed alexandrite laser. PIH incidence of 10% was found in the group treated with 532-nm Q-switched Nd:YAG laser[7].

A retrospective study of 516 patients with solar lentigines in South Korea has revealed overall incidence of PIH after treatment using a 532-nm Q-switched Nd:YAG laser to be 20.3%. Patients who had dyschromia, large pores, and velvety skin were reported to have higher risk of developing PIH[8].

Kim et al. conducted a randomized, controlled, split-face, comparative study using 532-nm picosecond Nd:YAG laser or 532-nm Q-switched Nd:YAG laser for the treatment of solar lentigines in 20 patients. The clearance of the lesions was significantly

better on the sides treated with the picosecond laser. Incidence of PIH was reported in 5% of the lesions treated with 532-nm picosecond Nd:YAG laser, and 30% in the group treated with or 532-nm Q-switched Nd:YAG laser[10].

Another comparative study was conducted in 25 Thai patients who had SPTs of III-IV, with solar lentigines on upper extremities, using either fractional CO_2 laser or 532-nm Q-switched Nd:YAG laser. The lesions treated with 532-nm Q-switched Nd:YAG laser has shown significantly better improvement, compared with the lesions treated with fractional CO_2 laser. PIH incidence was 24% in the group treated with 532-nm Q-switched Nd:YAG laser[4].

In conclusion, the incidence of PIH following 532-nm Q-switched Nd:YAG laser treatment for removal of solar lentigo lesions has been reported to range from 8.47-47% in previous studies, especially in people with darker skin types[4-10].

PIH Prophylaxis

In clinical practice, various strategies have been implemented in an attempt to reduce the occurrence of PIH after laser therapy[5]. However, current evidence of PIH prevention is limited. The prevention of PIH can be categorized into two main groups: pretreatment and posttreatment prophylaxis. Regarding pretreatment strategies, the published studies include the use of glycolic acid, retinoids, hydroquinone, and topical brimonidine, while the methods for preventing PIH after procedures include the use of sunscreen, topical corticosteroids, and tranexamic acid[17].

Pretreatment Prophylaxis

1. Glycolic Acid, Hydroquinone, and Retinoids

Glycolic acid is a naturally derived **α**-hydroxy acid that can be used for superficial peeling of the skin which results in skin lightening[96]. Hydroquinone inhibits the tyrosinase enzyme, thus, preventing the production of melanin. It also disrupts DNA and RNA synthesis, degrades melanosomes, and damages melanocytes[58]. Topical retinoids induce epidermal turnover and is also thought to inhibit tyrosinase enzyme[17]. However, evidence supporting the use of these agents is limited. West et al. conducted a study using 10% glycolic acid or 4% hydroquinone cream plus 0.025% tretinoin cream,

compared with no treatment, to prevent PIH following full-face CO_2 laser resurfacing. There was no difference regarding the occurrence of PIH between the treatment group and the control group[97].

Table 4 Glycolic acid, hydroquinone, and retinoids for PIH prophylaxis

Author, Year	Setting	Intervention	PIH prevention	Method	Results
West et al.[97], 1999	Randomized controlled trial, n=100, skin type I-III	Full face CO_2 resurfacing	Group 1: 10% glycolic acid cream bid (n=25), Group 2: 4% HQ cream hs plus tretinoin 0.025% cream bid (n=25) Control: no pretreatment (n=50)	- The interventions were applied for 2 weeks before the treatment - Clinical evaluation and photographic assessment for presence of PIH at week 4 and 12 posttreatment	- Incidence of PIH did not significantly differ between all regimens - No reported side effects

2. Topical Brimonidine

Topical brimonidine gel, a highly selective **α**-2 adrenergic agonist that causes potent vasoconstrictive effect on dermal blood vessels with a diameter of less than 200 μm, is indicated for a treatment of persistent erythema of rosacea in adults aged 18 years old and above[22, 98]. It was previously used to treat open-angle glaucoma. Brimonidine was also reported to have anti-inflammatory effect in a previous study using mouse ear models. It was found to significantly prevent induction of ear edema, compared with a control intervention[5, 99].

Brimonidine is metabolized in the liver and eliminated via urinary tract. Benkali et al. reported that systemic absorption occurred in 22–79% of patients who applied topical brimonidine for 29 days with mean peak serum level ranging from 13 to 25 pg/mL, which is much lower than the systemic absorption of brimonidine tartrate 0.2% eye drops 3 times a day, yielding average peak serum level of 54 pg/mL[100].

A few case reports have shown that topical brimonidine gel 0.33% may have a potential effect in reducing posttreatment erythema and PIH after laser therapy[23-25]. The mechanism by which topical brimonidine reduces PIH after laser treatment is not clearly understood. Previous studies in patients with solar lentigo and melasma suggested that increased blood flow and vascularity may be associated with hyperpigmentation[5, 26, 27]. Considering previous evidence reporting that endothelial cells can induce melanin synthesis, it is likely that microvasculature plays a role in the development of pigmentary disorders[33].

For the treatment of erythema, topical brimonidine was reported to have potent vasoconstrictive effects that block the vasodilation caused by capsaicin. These data are consistent with other publications which have demonstrated that brimonidine inhibited cutaneous vasodilation induced by temperature, suggesting the underlying mechanism of brimonidine on the treatment of erythema[101].

According to the FDA, topical brimonidine should be used with caution in patients with conditions that may lead to vascular insufficiency; including depression, cerebral or coronary artery infarction, orthostatic hypotension, Raynaud's phenomenon, scleroderma, Sjogren's syndrome, or thromboangiitis obliterans. Additionally, the patients with severe cardiovascular disease should also use topical brimonidine with caution due to the potential effects of brimonidine on the blood pressure[102].

Adverse effects of brimonidine that were most frequently reported in previous studies include erythema, flushing, burning, and contact dermatitis. The incidence of side effects was revealed to be at least 1% of the patients treated with topical brimonidine and the most common one was rebound erythema[98].

Table 5 Topical brimonidine for PIH prophylaxis

Author, Year	Setting	Intervention	PIH prevention	Method	Results
Hong et al.[24], 2018	Case report, split lesion study, n=1, 58 years old male with SLs, skin type IV	Q-switched 532-nm Nd:YAG laser	Intervention: 0.33% topical brimonidine gel applied on lesion (b), 1 hour pretreatment and applied posttreatment for 3 weeks Control: no pretreatment on lesion (a)	- Methyl prednisolone cream was applied on both lesions for 3 days posttreatment - Dermoscopic exam and photographic assessment at 3 weeks and 6 months posttreatment	- Lesion (a) left PIH - Lesion (b) showed no evidence of PIH and markedly decreased background erythema - No reported side effects
Lee et al.[25], 2019	Case series, n=2, Case 1: split-lesion study, 16 years old male, skin type IV Case 2: split-face study, 48 years old male, skin type IV	Case 1: 1064-nm picosecond Nd:YAG laser for tattoo removal Case 2: Q-switched ruby 694-nm laser for treatment of melasma	0.33% topical brimonidine gel	Case 1: 0.33% brimonidine gel was applied on the upper half of the tattoo 1 hour prior to treatment Case 2: topical brimonidine was applied to only the right side of the face 1 hour prior to treatment and applied for 3 days after the treatment	Case 1: less erythema, swelling, and discomfort in brimonidine-treated area, no commentary on PIH Case 2: PIH on the left side (not treated) and no PIH on the right side (treated site) 2 weeks after the laser treatment

Posttreatment Prophylaxis

1. Photoprotection

UV exposure is known to induce melanogenesis in melanocytes; therefore, photoprotection has become an important basis in the management of dyspigmentation. Wanitphakdeedecha et al conducted a study in 30 patients who received fractional CO_2 laser resurfacing and used broad-spectrum SPF 60+ sunscreen or petrolatum ointment as PIH prophylaxis. A significant reduction in melanin index was found only in the sunscreen group[20]. Nowadays, sunscreen application after laser therapy has become a part of routine clinical practice in most clinical settings.

Table 6 Photoprotection for PIH prophylaxis

Author, Year	Setting	Intervention	PIH prevention	Method	Results
Wanitphak-deedecha et al.[20], 2014	Randomized controlled trial, split-face study, n=30, Patients with boxscars on both sides of the face, skin type IV	Ablative fractional CO_2 resurfacing	- Intervention: petrolatum ointment QID plus broad-spectrum sunscreen with anti-inflammatory agents (Eucerin Sun Fluid SPF 60+; Beiersdorf, Hamburg, Germany) in the morning for 7 days, starting from the first day after laser treatment - Control: petrolatum ointment QID	- Beyond 7 days after the treatment, the sunscreen were applied on both sides of the face for 3 months - Melanin indexes were measured at baseline, week 1, 2, month 1, 2, and 3 posttreatment	A statistically significant difference in melanin index at 1-week post laser treatment between both sides was found

2. Topical Corticosteroids

PIH is developed as a result of inflammatory responses of melanocytes. This reaction can be generated by nonspecific thermal damage that occurred during laser therapy[5]. Excessive melanin production and irregular distribution of melanin pigments can be found in the skin following cutaneous inflammation[96]. An increase in melanocyte function is thought to result from a stimulation by cytokines, prostanoids, chemokines, reactive oxygen species, and other inflammatory mediators that are produced during the process of inflammation[19]. A previous study has suggested that prostaglandin E2, leukotriene C4 and thromboxane B2 may be accountable for the development of PIH[14].

Topical corticosteroids are indicated for the treatment of inflammatory or pruritic skin conditions[5]. Their mechanisms of action consist of anti-inflammatory, anti-proliferative, vasoconstrictive, and immunosuppressive effects. Corticosteroids inhibit phospholipase A2, inhibit inflammatory transcription factors, and prevent the cell membrane from releasing arachidonic acid and platelet activating factors; consequently, they inhibit the production of inflammatory mediators, including prostaglandins and leukotrienes[14]. Therefore, anti-inflammatory effects of topical corticosteroids may potentially benefit the prevention of PIH after laser therapy. Moreover, the vasoconstrictive properties may result in reducing the occurrence of posttreatment erythema[5].

Takiwaki et al. has reported that topical clobetasol propionate was the most potent agent that suppressed erythema and pigmentation induced by UVB. The second and the third most potent agents were hydrocortisone butyrate and indomethacin, respectively. However, the anti-proliferative effect of corticosteroids may affect fibroblast activity, which can further impair the formation of new collagen[103].

Cheyasak et al. conducted a study using topical clobetasol propionate 0.05% ointment in the prevention of PIH after ablative fractional CO_2 laser resurfacing in 40 Asians with atrophic acne scars and SPTs IV. One side of the face was treated with clobetasol propionate twice a day for 2 days, while the other side was treated with petrolatum jelly 4 times per day. A significantly higher incidence of PIH was found on the side treated with petrolatum jelly (75%), compared with the side treated with topical

clobetasol (40%)[5]. However, the duration of erythema was not different between the two groups. 7.5% of the patients developed acneiform eruption. No other adverse reactions were noted[19].

The adverse reactions of topical corticosteroids can occur locally or systemically. Local adverse effects usually occur following continuous treatment in the same region, depending on the potency, vehicle, and site of application. The most common local adverse effects are skin atrophy, striae, perioral dermatitis, acne, rosacea, and purpura. Local adverse effects that are less likely to occur include hypertrichosis, pigmentary changes, and poor wound healing[104]. Systemic adverse effects are uncommon; however, they can occur with the persistent use of high-potency corticosteroids on the thin skin. The reported systemic side effects include hypothalamic-pituitary axis (HPA) suppression, avascular necrosis of femoral head, glaucoma, growth retardation in children, Cushing syndrome, hyperglycemia, hypertension, and systemic infections[104, 105].

The treatment with clobetasol propionate (0.05%) in a dose of 2 gram daily for a few days can result in decreased morning cortisol level[106] and the use of more than 100 gram per week can lead to iatrogenic Cushing syndrome and adrenal insufficiency[107]. Allenby *et al.* has demonstrated that adrenal suppression can occur following the use of topical clobetasol propionate exceeding 50 gram per week[108]. To avoid side effects, the treatment with topical corticosteroids of all potencies should not be longer than 2-4 weeks. High-potency topical corticosteroids should not be applied for more than 2 weeks[109].

Table 7 Topical corticosteroids for PIH prophylaxis

Author, Year	Setting	Intervention	PIH prevention	Method	Results
Uaboonkul et al.[110], 2012	Randomized controlled trial, split-face study, n=25, Patients with symmetric facial Hori nevus on both cheeks	Q-switched Nd:YAG 1064 nm laser	- Intervention: fucidic acid combined with betamethasone valerate cream (Fucicort cream®) - Control: fucidic acid (Fucidin cream®) alone	- Each topical agent is applied to the designated side of the face for 2 weeks - Melanin indexes and photographic assessment by dermatologists at baseline, week 2, and week 4 posttreatment	- Melanin index did not significantly differ between both sides - The control side showed increased PIH by 2nd week post-laser, and cumulative increase in pigmentation at the 4th and 8th weeks (not statistically significant)
Cheyasak et al.[19], 2015	Randomized controlled trial, split-face study, n=40, Patients with facial atrophic acne scars, skin type IV	Fractional CO_2 resurfacing	- Intervention: clobetasol propionate 0.05% ointment BID for the first 2 days, - Control: petrolatum jelly alone QID for 7 days	Melanin index, clinical, and occurrence of PIH assessed once weekly for first month, then monthly up to 3 months.	The control side had significantly higher incidence of PIH posttreatment and significantly higher PIH intensity/surface area

3. Topical Corticosteroids Under Occlusion

Occlusive dressings have been used to increase the therapeutic effects of topical corticosteroids since 1961[111]. Occlusion by any methods increases the

temperature and hydration of stratum corneum; therefore, it improves the absorption of topical corticosteroids. Several studies using topical corticosteroids with occlusive dressings, including plastic film, cellophane tape, occlusive tape (Blenderm), adhesive bandages (Band-Aid), and hydrocolloid dressings (HCD), have demonstrated an increase clearance of psoriatic lesions[112-116].

A previous study was conducted in 8 patients who had psoriasis, using clobetasol propionate, 0.1% betamethasone valerate, 0.1% triamcinolone, and 1% hydrocortisone under HCD (Actiderm) for 1 week. The lesions treated with first three regimens showed clearing of lesions within 1 week in 50% of the patients, while the other half of the patients had mild residual erythema[117].

McKenzie and Stoughton reported that using topical corticosteroids under occlusion can increase the vasoconstrictive effects 100-fold[118]. However, an in vivo study has shown only tenfold increase in efficacy of topical steroids when applied on the forearm under 96-hour occlusion[21].

Although the therapeutic effect of topical corticosteroids under occlusion has been reported to be excellent, it can also increase the risk of developing adverse effects. Cushing syndrome has been reported with the use of triamcinolone acetonide 0.1% in a dose of 38 gram per day under occlusion for 4 years[105].

Unlike the abundant publications investigating the effects of topical steroids under occlusion on psoriatic lesions, there is currently lack of evidence of PIH prophylaxis using this method. Considering the ability to enhance therapeutic effects of topical steroids with occlusive dressings, they may also have potential benefits in the use of PIH prevention.

4. Tranexamic Acid

Tranexamic acid (TA) or trans-4-aminomethylcyclohexanecarboxylic acid is a lysine analog and a plasmin inhibitor that prevents plasminogen from binding to the lysine binding site[119]. It is commonly used to prevent bleeding during surgical procedures. Topical TA has been demonstrated to inhibit UV-induced melanin production in guinea pigs[120] and intradermal injection of TA has been reported to be effective in the

treatment of melasma[119]. Topical TA has an inhibitory effect on UV-induced plasmin activity, which results in a suppression of arachidonic acid, prostaglandins, and tyrosinase activity. Therefore, TA can prevent UV-induced pigmentation[121]. Three-month administration of oral TA has also been reported to be effective in the treatment of melasma[122]. Studies using TA for posttreatment PIH prophylaxis have been conducted. TA was administered orally (750 and 1500 mg daily) or intradermally. None of the studies has found a significant reduction in the occurrence of PIH after laser therapy in the TA groups, compared with the control groups[121, 123, 124].

Table 8 Tranexamic acid for PIH prophylaxis

Author, Year	Setting	Intervention	PIH prevention	Method	Results
Sirithanabadee-kul et al.[124], 2018	Randomized controlled trial, split-lesion study, n=25, Patients who had at least 2 solar lentigines on their forearms, skin type III-V	Q-switched 532-nm Nd:YAG laser	- Intervention: TA intralesional injection (50 mg/mL) 0.1 mL/cm^2 per lesion - Control: 0.9%NSS	- Vaseline® was applied to all of the lesions BID until the crusts peeled off, followed by the application of broad-spectrum sunscreen with SPF of 40 for 12 weeks. - Melanin indexes and photographic assessment by dermatologists at baseline, week 2, 4, 8, and week 12 posttreatment	PIH rates were 16% in TA group and 28% in control group; however, the difference was not statistically significant between both groups

Table 8 (Continued)

Author, Year	Setting	Intervention	PIH prevention	Method	Results
Kato et al.[121], 2011	Randomized controlled trial, n=32, patients with SLs	694.5-nm Q-switched ruby laser	- Intervention: oral TA 750 mg daily for 4 weeks after treatment - Control: no treatment	- Clinical and colorimetric assessment were done and relative melanin values were obtained at baseline, week 2, and week 4 posttreatment	- The lesions were effectively cleared at week 2 and PIH was seen at week 4. - No significant difference in the incidence of PIH was found between both groups
Rutnin et al.[123], 2019	Randomized controlled trial, n=40, Patients with SLs, skin type IV	Q-switched frequency doubled 532-nm Nd:YAG laser	- Intervention: oral TA 1,500 mg daily for 6 weeks - Control: placebo for 6 weeks	- Ice pack compression was applied immediately after the treatment for 5 minutes. - Petrolatum ointment was applied to the treated area twice daily until the crusts peeled off. - Melanin index, photographic assessment, and dermoscopic exam by dermatologists at baseline, week 2, 4, 6, and 12 posttreatment	Incidence of clinical PIH was not significantly different between the 2 groups

5. Skin Cooling

Skin cooling has been commonly used to protect superficial skin layer during various laser therapy. It allows for the selective destruction of target chromophores while minimizing epidermal damage, improves tolerability of the procedures, decreases edema after treatment, allows for the use of greater fluences, and increases safety of the treatment in patients with darker skin types[125, 126]. The principal of skin cooling is the spatial selectivity of the cooling. The decreased temperature of the epidermis should be achieved by the cooling methods, whereas the temperature of target structures such as stem cells, matrix cells of the hair follicle, or blood vessel, should not be affected by the skin cooling[125].

Skin cooling methods consist of pre-cooling, parallel cooling, and post-cooling, and can be categorized into contact cooling and non-contact cooling. Contact cooling consists of active and passive method[126].

Active contact cooling is a highly effective cooling method that can be done by using copper or sapphire tips, which can be used to cool the skin before, during, and after the treatment. It is most beneficial for laser treatment with longer pulse durations, particularly if longer than 10 ms. However, the disadvantages of this method include the expensive cost of the handpiece, lasers, and cooling agents[126].

Passive contact cooling can be done before, during, or after laser treatment with ice packs or ice cubes. It is an easy, cheap, and user-friendly method that can be used to reduce edema and inflammation after dermatologic procedures. The ice packs are advised to be placed on the skin until the pain or redness disappears. Epidermal temperature of 12°C can be achieved after cooling for 10 seconds. The ice packs can be used on large areas, while the ice cubes are more suitable for smaller areas. The disadvantages of this method of cooling include the formation of bubbles on the skin and a discomfort caused by the melting water[126].

Non-contact skin cooling can be achieved by cryogen spray, dynamic skin cooling, or cold air. The cryogen spray is advised to be used at a distance of 20 cm from the surface of the skin. Nowadays, it is not recommended due to high risk of skin

necrosis. The dynamic cooling device (DCD) was developed to reduce the adverse reactions, using pulsed cryogen spray as the cooling agent. It is indicated for laser treatment with pulse durations shorter than 5 ms. The advantage of the DCD is that it selectively cools the skin within the depth of 200 μm from the skin surface. Therefore, it allows for the use of high fluences with good safety profile. The disadvantage of this method is that it is ineffective when the pulse durations are longer than 10 ms. In addition, it can cause damage to the ozone layer as it contains fluoroethane[126].

Cold air cooling can be used as pre-, parallel, or post-cooling method without interfering with the laser irradiation. It can be used to ease the pain and reduce thermal injury caused by the procedures. Moreover, it is compatible with all laser devices and provides good comfort to the patients.

In clinical practice, the use of skin cooling for PIH prevention is common. It is thought to reduce the risk of PIH by minimizing collateral thermal injury caused by the laser therapy. However, Manuskiatti et al. demonstrated that the use of cold air 30 seconds before, during, and 30 seconds after 1064-nm Q-switched Nd:YAG laser treatment of Hori nevus is associated with increased incidence of PIH. The underlying mechanisms of the induction of pigmentation by cold air are not well understood. It is possibly related to inherited chromatic tendency of each individual that allows for the variable responses of melanocytes to the stimuli such as inflammation, skin injury, or cold temperature[127].

Table 9 Skin cooling for PIH prophylaxis

Author, Year	Setting	Intervention	PIH prevention	Method	Results
Manuskiatti et al.[127], 2007	Randomized controlled trial, spit-face study, n=21, Patients with Hori nevus, skin type III-IV	Q-switched 1064-nm Nd:YAG laser	- Intervention: cold air cooling device (CRIOjet AIR Mini) was used at a cooling level of 4 - Control: no cooling	- The cooled side was always cooled during and 30 seconds before and after laser irradiation - The skin surface temperature was 4°C to 5°C - Melanin index and photographic assessment by dermatologists at baseline, week 1, 2, 3, 4, and 12 posttreatment	The cooled sides were significantly more likely to become hyperpigmented after laser irradiation than the uncooled side
Chan et al.[72], 2007	Retrospective study, spit-face study, n=37, Chinese Patients underwent therapy for acne scarring or skin rejuvenation	Fractional resurfacing 1,540-nm Erbium glass laser (Fraxel SR)	- Intervention: Air cooling was used in the treatment that took place between March 1 and May 31 - Control: no cooling	- The patients who underwent therapy for acne scarring were given a high energy but low density treatment, and those who underwent skin rejuvenation were given a low energy but high density treatment. - Clinical photographs were assessed pre- and post-treatment for evidence of PIH	Localized PIH occurred in the peri-oral area among patients who did not receive air cooling as an adjunctive therapy

In summary, this review of literature shows the lack of standard prevention of PIH. In regard to pretreatment PIH prophylaxis, topical glycolic acid, hydroquinone, and tretinoin were found to be ineffective in reducing the incidence of PIH. The case reports of PIH prevention using topical brimonidine revealed potential effects of brimonidine in reducing erythema and PIH after laser therapy. However, the data were only obtained from 3 patients. Therefore, this study aims to further investigate the efficacy of topical brimonidine in reducing the incidence of PIH after laser procedures.

For the posttreatment PIH prophylaxis, photoprotection and topical corticosteroids have been demonstrated to reduce the risk of PIH after laser treatment. Sunscreen application after laser therapy has become a part of routine clinical practice in most clinical settings and is supported by evidence. Topical corticosteroids, as well as topical steroids under occlusion, are also widely use in clinical practice following laser therapy and were reported to reduce the incidence of PIH. However, the evidence is currently sparse and controversial. Therefore, the goal of this study is also to evaluate the efficacy of topical corticosteroids and topical steroids under occlusion in preventing PIH after laser therapy.

CHAPTER 3
RESEARCH METHODOLOGY

Research Design

An experimental, prospective, randomized, single-blinded, controlled, intra-individual, comparative study.

Target Population

Patients who had at least 8 solar lentigines on the forearms and underwent one session of Q-switched Nd:YAG 532 nm laser treatment at Srinakharinwirot university skin center.

Sample Size Calculation

Sample size was calculated by two dependent proportions formula, using N4Studies program.

In previous study, the incidence of PIH following laser treatment of pigmented lesions on the side of the face treated with topical clobetasol was 40% (0.4), while the incidence of PIH on the controlled side of the face was 75% (0.75)[5, 19].

Setting errors as follows: α = 0.05, β = 0.2 (Power = 0.8)

The ratio of control to experimental groups was 1:1

Sample size estimation = 72 lesions per each intervention

After adjusting for a dropout rate of 10%, the total number of lesions needed for the study was estimated to be 80 lesions per each intervention.

Therefore, if each patient has 8 lesions (2 lesions in each treatment area), the number of subjects needed for the study would be 40 persons.

Sampling Strategy

The participants were selected from the population using a consecutive sampling technique.

Randomization

Treatment allocation was done using a computer-generated block randomization with a block size of 4. Different sets of blocks with random sequences of treatment were generated and were applied to each patient according to their subject ID. The lesions in each area were allocated to receive topical corticosteroids, topical corticosteroids under occlusion, topical brimonidine, or petrolatum jelly[5].

Allocation Concealment

The dermatologists who performed subjective evaluation were unaware of the methods of prophylactic treatment used in each area of the forearm.

Inclusion Criteria

1. Male or female subjects above 18 years of age

2. Subjects who had at least 8 solar lentigines on the forearms (diagnosed clinically or dermoscopically by a dermatologist). The lesions should be located on 4 different areas of the forearms; including left upper forearm, left lower forearm, right upper forearm, and right lower forearm; and there should be at least 2 lesions in each area.

3. Subjects who were willing to attend the project and signed informed consent form

Exclusion Criteria

1. Subjects who had active inflammatory diseases or infections at the site of treatment

2. Subjects who had photosensitive skin conditions

3. Subjects with a history of hypertrophic scars or keloids

4. Subjects with a history of skin malignancy

5. Subjects who received topical retinoids, hydroquinone, chemical peeling, or other topical whitening agents on the forearms within a period of 1 months prior to treatment

6. Subjects who received oral retinoids within 6 months prior to treatment

7. Subjects who underwent non-ablative laser therapy on the forearms within a period of 3 months prior to treatment

8. Subjects who underwent ablative laser therapy on the forearms within a period of 6 months prior to treatment

9. Subjects who were allergic to topical analgesics, topical corticosteroids, topical brimonidine, petrolatum jelly, or other inactive ingredients of the medication such as propylene glycol, paraffin, sorbitan sesquioleate, carbomer, methylparahydroxybenzoate, phenoxyethanol, glycerol, titanium dioxide, and sodium hydroxide

10 Subjects who had conditions that should avoid using topical brimonidine; including cerebral or coronary artery infarction, orthostatic hypotension, Raynaud's phenomenon, scleroderma, Sjogren's syndrome, thromboangiitis obliterans, and severe cardiovascular disease

11. Subjects who had coagulation disorders

12. Subjects who were pregnant or lactating women

13. Subjects who were likely to have impaired wound healing such as smokers or patients with poorly-controlled diabetes mellitus

Discontinuation Criteria

1. Subjects who develop serious adverse events (SAEs), including death, life-threatening events, hospitalization, disability, or significant permanent damages during the study

2. Subjects who develop adverse reactions that require discontinuation of the study such as ulceration or scarring

3. Subjects who unable to assess the primary outcome of the study

4. Subjects who request to quit the program

Research Instruments

1. Agents used in the regimens for PIH prophylaxis:

1.1 Topical clobetasol propionate 0.05% ointment (Dermovate®,

GlaxoSmithKline UK, Middlesex, United Kingdom) which contains propylene glycol, white soft paraffin, and sorbitan sesquioleate as inactive ingredients

1.2 Tegaderm (3M, St Paul, Minnesota) as an occlusive dressing

1.3 Topical brimonidine tartrate 0.33% gel (Mirvaso®; Galderma, Lausanne, Switzerland) which contains carbomer, methylparahydroxybenzoate (e218), phenoxyethanol, glycerol, titanium dioxide, propylene glycol, sodium hydroxide, and purified water as inactive ingredients

1.4 Petrolatum jelly (Vaseline®)

2. Topical anesthetic cream: lidocaine 2.5% and prilocaine 2.5% cream (Racser® cream, Galentic Pharma, India)

3. Broad-spectrum sunscreen with sun protection factor (SPF) 50+

4. 532-nm Q-switched Nd:YAG laser device (Medlite C6; HOYA ConBio, Fremont, CA, USA)

5. Dermatoscope

6. Mexameter® MX18 (Courage-Khazaka, Electronik, Köln, Germany)

7. High-resolution digital camera Fujifilm X-T30 with attached Fujifilm Fujinon XF 18-55 mm f/2.8-4.0 R LIM OIS lens

8. Photography light box

9. Plastic sheets and a permanent marker used for locating each lesion and each area of treatment

10. Case record form (CRF) that contains

10.1 Study record form

10.2 Adverse reactions and wound healing record form

10.3 Patient satisfaction self-evaluation form

11. Patient information sheet

12. Informed consent form

13. Patient's logbook for recording adverse reactions

Data Collection Process

Screening Visit

After selection of subjects according to inclusion and exclusion criteria, the patients were informed about objectives of the study, research method, potential benefits, and possible adverse outcome from the study. Written informed consent was obtained from each patient before enrollment. Patient history; including general history, past health history, current medications, and drug allergy, were obtained. Dermatologic examination was performed to assess the Fitzpatrick's skin phototypes (SPTs) of the patients. Baseline information of the patients was recorded in the case record from. Information regarding pregnancy, last menstrual period, and lactation were obtained from female patients.

Table 10 The Fitzpatrick's classification of skin phototypes[128]

Skin phototypes	Color of unexposed skin	Burning and tanning upon sun exposure
I	Pale white	Always burns, never tans
II	White	Always burns, then tans
III	White	Sometimes burns, can tan without prior burn
IV	Light brown	Usually does not burn, tans easily
V	Brown	Rarely burns, tans easily
VI	Dark brown to black	Burns only with very high UVR doses, tans

Enrollment Visit (Baseline; Week 0)

After the process of screening, the skin of the forearms of the patients was cleansed with mild cleanser. Subject ID was written on the right lower corner of a plastic sheet, then the plastic sheet was placed on both forearms of the patient. After that, the outline of the forearm and each area of treatment were drawn on the plastic sheet. The treatment areas were divided into 4 areas; left upper forearm area, left lower forearm area, right upper forearm area, and right lower forearm area, as demonstrated in figure 11. Two most prominent lesions in each area of treatment were selected. The position and number

of each lesion were marked on the plastic sheet. Additionally, the marker of each area of treatment were drawn on the forearms of the patients using a marker.

Digital photographs of the lesions were taken with high-resolution digital camera (Fujifilm X-T30) with attached Fujifilm Fujinon XF 18-55 mm f/2.8-4.0 R LIM OIS lens to determine the baseline characteristics of each lesion. For each patient, images of the selected lesions were taken, along with the photographs of each treatment area and both forearms. The patients were instructed to place their forearms in a photography light box. All of the photographs were taken under the same lighting conditions, with the same camera settings. The file code of the photographs and date of photo-shoot were recorded in the study record form.

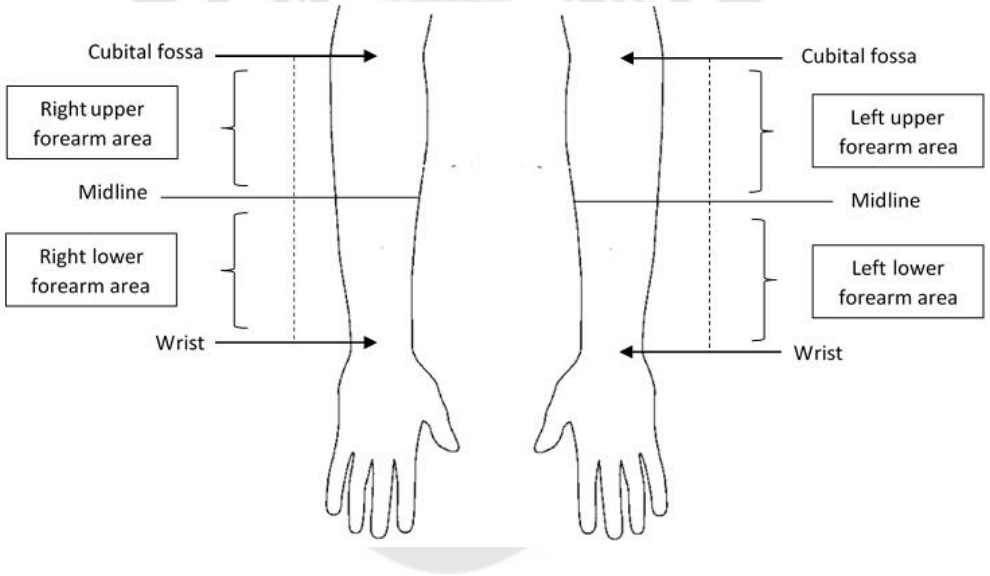


Figure 11 Areas of treatment

Baseline melanin index and erythema index of each lesion were assessed by Mexameter® MX18. The measurement was performed 3 times on each lesion and the average values of melanin and erythema indices were calculated[5].

Treatment allocation was done using a computer-generated block randomization with a block size of 4. The lesions in each area received intervention A, B, C, or D, in random sequences. The lesions in the area allocated to receive prophylactic

treatment A were applied with topical clobetasol propionate 0.05% ointment twice daily for 2 days after laser treatment. The lesions in the area allocated to receive prophylactic treatment B were applied with topical clobetasol propionate 0.05% ointment under occlusive dressings (Tegaderm; 3M, St Paul, Minnesota) for 24 hours after laser treatment. The lesions in the area allocated to receive prophylactic treatment C were applied with topical brimonidine tartrate 0.33% gel 1 hour before and 3 days after laser treatment. And the lesions in the area allocated to receive prophylactic treatment D received petrolatum jelly 4 times a day for 7 days, as a control intervention. After applying the prophylactic treatment as instructed, petrolatum jelly was applied to all lesions 4 times a day until 7 days after laser treatment[5]. (Table 11)

Table 11 Summary of prophylaxis regimens for PIH

Intervention	Topical medications used	*Directions* for the *application*
A	Topical clobetasol propionate 0.05% ointment	Applied twice daily for 2 days
B	Topical clobetasol propionate 0.05% ointment under occlusive dressings (Tegaderm)	Applied 24 hours after laser therapy
C	Topical brimonidine tartrate 0.33% gel	Applied 1 hour prior to laser therapy and once daily for 3 days after laser therapy
D	Petrolatum jelly (control)	Applied QID for 7 days

Lidocaine 2.5% and prilocaine 2.5% cream (Racser® cream), as well as topical brimonidine, were applied to the lesions 1 hour prior to treatment. All lesions on both forearms were treated with a single session of 532-nm Q-switched Nd:YAG laser, using a spot size of 3 mm, energy fluences of 0.8–1.8 J/cm^2, at a frequency of 2 Hz. The parameters of laser were adjusted until the clinical endpoint of immediate whitening was observed. After laser therapy, digital photographs were taken and each topical prophylactic agents were applied to the lesions. The patients were instructed to use a

broad-spectrum sunscreen with a sun protection factor of 50 and were advised to avoid sun exposure until the end of the study[5].

After the treatment, each patient received 3 units of 5-gram similar plastic containers; each of which contains topical clobetasol propionate 0.05% ointment, topical brimonidine tartrate 0.33% gel, or petrolatum jelly. The instruction and area of application were labeled on each container. Detailed instructions on how to apply each topical medication for PIH prophylaxis and the potential adverse reactions were given to the patients[5]. The patients were instructed to record the duration of downtime and all of the adverse effects in the logbook. If there were any concerns or if any adverse reactions occurred, the patients were advised to inform the researcher. Follow-up visits were appointed at 2, 4, 8, and 12 weeks after treatment[5].

Follow-Up Visits (Week 2, 4, 8, and 12)

After general history had been taken, the skin of the forearms was cleansed with mild cleanser. The previously marked plastic sheet of each patient was placed on the forearms to locate the previously selected lesions and the marker of each treatment area would be drawn on the skin.

Digital photographs of the lesions were taken with the previously used camera and lens to determine the changes of the lesions in each treatment area. For each patient, photographs of each selected lesion were taken, along with photographs of each treatment area, and 1 photo of both forearms. The patients were instructed to place their forearms in the same photography light box as the enrollment visit. All of the photos were taken under the same lighting conditions, with the same camera settings. The file code of the photographs and date of photo-shoot were recorded in the study record form.

Masked assessment of the occurrence of PIH, degree of PIH, degree of erythema, and improvement of lesions, were subjectively evaluated in each follow-up visit from the digital photographs by 2 dermatologists[5].

The melanin index and erythema index of the selected lesions in each area were assessed by Mexameter® MX18 in every follow-up visit to determine the intensity of PIH and erythema after laser treatment[5].

In addition, the patients were asked to evaluate their satisfaction score at the end of the study and record the observable adverse reactions in each follow-up visit. If any adverse reactions occurred, the participants would be treated without any additional fee. In case of persistent PIH, the patient would be treated with 4% Hydroquinone until recovery or until the patient is satisfied.

Co-Intervention

Photoprotection was recommended throughout the study. The patients were instructed to use a broad-spectrum sunscreen with a sun protection factor of 50 and were advised to avoid sun exposure until the last follow-up visit[5]. Routine shower with gentle cleanser was recommended after 24 hours following laser therapy. All participants were instructed not to receive other treatments, including laser therapy, chemical peeling, and topical lightening agents, on the forearms throughout the study.

Outcome Measurement

Primary Outcome

The primary outcome of this study is the occurrence of PIH. According to the study conducted by Kato et al.[121], the treatment-related crust usually came off at approximately 1 week, the pigmentation of solar lentigines were typically improved at 2 weeks, and the PIH was most commonly observed at 4 weeks after laser treatment. In some cases, the PIH can be observed at 8 weeks or more. In this study, the occurrence of PIH was defined as an increase in pigmentation, at the area where the lesions were previously located, after the crust had fallen off following a laser treatment. Masked assessment was subjectively evaluated from the digital photographs by dermatologists at 2, 4, 8 and 12 weeks after laser treatment and the results were reported as no PIH or presence of PIH[5].

Secondary Outcome

1. Intensity of PIH was evaluated after laser treatment by the following methods:

1) Subjective assessment was performed at 2, 4, 8 and 12 weeks after laser treatment by 2 dermatologists. The degree of PIH was evaluated from the digital photographs using a 5-point grading scale, which consists of grade 0, no PIH; grade 1, barely visible PIH (1-25% darkening of pigmentation); grade 2, mild PIH (26-50% darkening of pigmentation); grade 3, moderate PIH (51-75% darkening of pigmentation); and grade 4, severe PIH (76-100% darkening of pigmentation); as demonstrated in Figure 12 and Table 12.

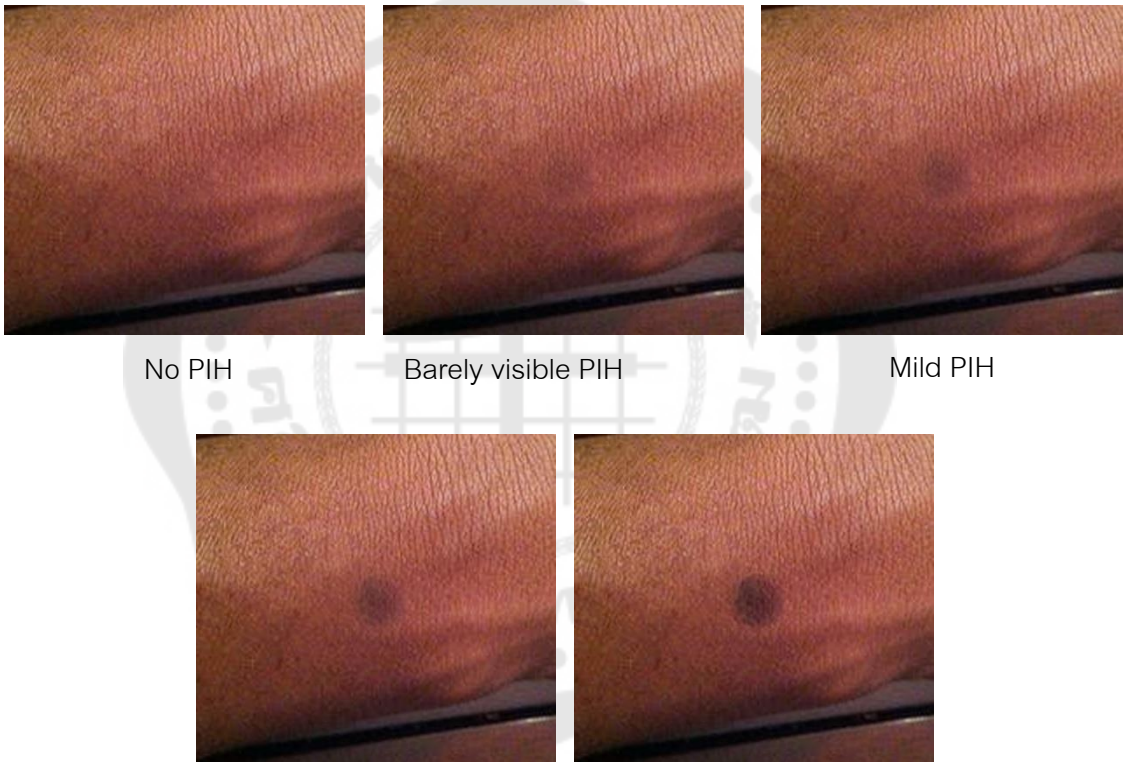


Figure 12 Degree of PIH

Table 12 5-point grading scale for degree of PIH assessment

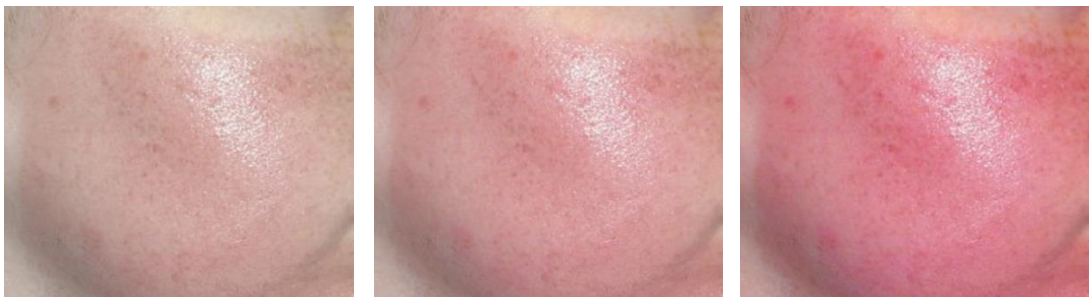
Grade	Degree of PIH	Characteristics
0	No PIH	No darkening of pigmentation
1	Barely visible PIH	1-25% darkening of pigmentation
2	Mild PIH	26-50% darkening of pigmentation
3	Moderate PIH	51-75% darkening of pigmentation
4	Severe PIH	76-100% darkening of pigmentation

2) Objective assessment of melanin index of the selected lesions in each area was measured using Mexameter® MX18 at baseline, and 2, 4, 8 and 12 weeks after laser treatment. The measurement was performed 3 times on each lesion and the average values of melanin index were calculated[5]. During the measurements, the room temperature should be 20°C and relative humidity should be 40-60%. The probe was placed perpendicular to the skin and gentle pressure was applied.

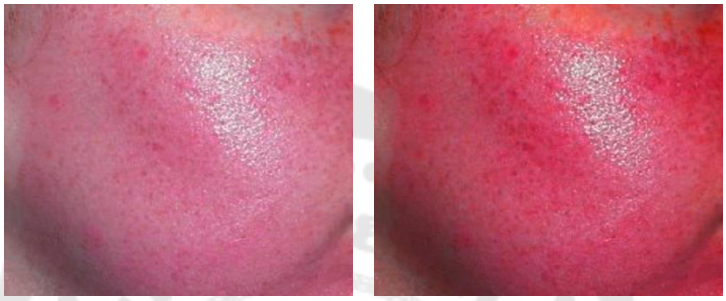
Mexameter provides rapid assessment; only 1 second is needed for the results to be obtained[93]. It was reported to perform well regarding sensitivity and reproducibility[94]. 660-nm wavelength allows for the avoidance of the interference by other components such as bilirubin[86]. Mexameter reports values in a quantitative scale of 0-999 for melanin indices; thus, even the slightest alteration in color can be detected.

2. Erythema in each area was assessed after laser treatment by the following methods:

1) Subjective assessment of erythema was performed at 2, 4, 8 and 12 weeks after laser treatment by 2 dermatologists from the digital photographs using a 5-point grading scale for degree of erythema, which consists of grade 0, no erythema; grade 1, barely visible erythema (1-25% skin redness); grade 2, mild erythema (26-50% skin redness); grade 3, moderate erythema (51-75% skin redness); and grade 4, severe erythema (76-100% skin redness); as demonstrated in Figure 13 and Table 13.



No erythema Barely visible erythema Mild erythema



Moderate erythema Severe erythema

Figure 13 Degree of erythema

Table 13 5-point grading scale for degree of erythema assessment

Grade	Degree of erythema	Characteristics
0	No erythema	No skin redness
1	Barely visible erythema	1-25% skin redness
2	Mild erythema	26-50% skin redness
3	Moderate erythema	51-75% skin redness
4	Severe erythema	76-100% skin redness

2) Objective assessment of erythema index of the selected lesions in each area was measured using Mexameter® MX18 at baseline, and 2, 4, 8 and 12 weeks after laser treatment. The measurement was performed 3 times on each lesion and the average values of melanin index were calculated[5].

3. Assessment of improvement of lesions was performed at 2, 4, 8 and 12 weeks after treatment using a 5-point grading scale, which consists of grade 0, none (no improvement or worsening of lesions); grade 1, poor (1-25% improvement); grade 2, fair (26-50% improvement); grade 3, good (51-75% improvement); and grade 4, excellent (76-100% improvement); as demonstrated in Table 14. The assessment was done by clinical evaluation from the digital photographs by 2 dermatologists.

Table 14 5-point grading scale for improvement of lesions assessment

Grade	Improvement of lesions	Characteristics
0	None	No improvement or worsening of lesions
1	Poor improvement	1-25% improvement
2	Fair improvement	26-50% improvement
3	Good improvement	51-75% improvement
4	Excellent improvement	76-100% improvement

4. Patient satisfaction in various aspects, including improvement of the lesions, patient's convenience, sensation after applying each PIH prophylactic treatment, and overall patient satisfaction, were evaluated at the end of the study by the patients using a 5-point grading scale, which consists of grade 1, very dissatisfied; grade 2, somewhat dissatisfied; grade 3, neither satisfied nor dissatisfied; grade 4, somewhat satisfied; and grade 5, very satisfied; as demonstrated in Table 15.

Table 15 5-point grading scale for patient satisfaction score

Grade	Patient satisfaction
1	Very dissatisfied
2	Somewhat dissatisfied
3	Neither satisfied nor dissatisfied
4	Somewhat satisfied
5	Very satisfied

5. Adverse reactions, including burning, itching, dryness, scaling, eczematous reaction and other reactions, were recorded immediately after treatment, and at 2, 4, 8 and 12 weeks after treatment.

6. Assessment of duration of wound healing process was subjectively evaluated immediately after laser treatment, and at 2 and 4 weeks in terms of duration of pain, crusting, edema, and erythema. The data were recorded in the patient's logbook.

Table 16 Summary of data collection process

Process	Visits				
	Baseline	Week 2	Week 4	Week 8	Week 12
1. Subject selection based on inclusion and exclusion criteria	/				
2. Patients were informed about objectives of study, research method, and potential benefits of the study	/				
3. Informed consent	/				
4. Basic information obtained from the patients	/				
5. Randomization	/				
6. Digital photographs	/	/	/	/	/
7. 532-nm Q-switched Nd:YAG laser treatment of solar lentigines	/				
8. Application of topical agents for PIH prophylaxis	/				
9. Subjective outcome measurement					
- Occurrence of PIH		/	/	/	/
- Intensity of PIH		/	/	/	/
- Degree of erythema		/	/	/	/
- Improvement of lesions		/	/	/	/

Table 16 (Continued)

Process	Visits				
	Baseline	Week 2	Week 4	Week 8	Week 12
10. Objective outcome measurement					
- Melanin index from Mexameter	/	/	/	/	/
- Erythema index from Mexameter	/	/	/	/	/
11. Patient satisfaction					/
11. Record of adverse reactions	/	/	/	/	/
12. Record of duration of wound healing	/	/	/		

Data Analysis

Descriptive Statistics

Categorical variables were demonstrated using numbers and percentages, while continuous variables were demonstrated using mean value and standard deviation (SD) or median and interquartile range (IQR), for the data with normal distribution and non-normal distribution, respectively[5].

Inferential Statistics

Linear mixed model was used to compare the continuous outcome between each method of PIH prophylaxis[5]. Survival analysis was used for analyzing the relationship between each intervention and the occurrence of PIH at each week. Pearson's Chi-square test was used to assess the significance of the difference of categorical data between each group.

In case of non-adherence to the protocol, for example, the patients received co-interventions, or did not apply the prophylactic treatment as instructed, intention-to-treat analysis would be used to analyze each intervention as previously randomized.

All statistical analyses were performed using Stata 17 (StataCorp., 2021; Stata Statistical Software, College Station, TX: StataCorp LLC). $P<0.05$ would be considered statistically significant[5].

CHAPTER 4
RESULT

This experimental, prospective, randomized, single-blinded, controlled, intra-individual, comparative study was conducted with the aim to determine the efficacy of various prophylactic interventions which have potential benefits in preventing PIH following solar lentigines removal using 532-nm Q-Switched Nd:YAG laser. In this study, the PIH prophylactic regimens were as follows: 2-day application of topical clobetasol propionate 0.05% ointment (Group A), 24-hour application of topical clobetasol propionate 0.05% ointment under occlusion (Group B), 1-hour pretreatment and 3-day posttreatment application of topical brimonidine tartrate 0.33% gel (Group C), and 7-day application of petrolatum jelly as control (Group D). The research protocol was reviewed and approved by Srinakharinwirot University Ethics Committee for Human Research (Approval number; SWUEC/F-352/2564) and was registered in Thai Clinical Trials (TCTR20231024002)[5]. Data collection was conducted during May to December, 2022. Written consent was obtained from all participants.

In this chapter, the results of the study will be summarized as follows:

1. Baseline characteristics
2. Occurrence of PIH
3. Intensity of PIH
4. Degree of erythema
5. Improvement of lesions
6. Patient satisfaction
7. Adverse reactions
8. Duration of wound healing process

Baseline characteristics

A total of 38 participants who had at least 8 solar lentigines on the forearms were enrolled in the trial according to inclusion and exclusion criteria. However, 1 subject requested to withdraw from the study due to inability to follow-up and 1 subject was discontinued due to failure to evaluate the primary outcome, thus, a total of 36 subjects completed the study, with a total of 288 lesions, each group containing 72 lesions. Baseline characteristics of the participants are as shown in Table 19. The subjects were 3 males (8.33%) and 33 females (91.67%). Ages of the patients ranged from 29 to 69 years old and the median age (IQR) was 58.5 (53.65) years old. The majority of the patients (58.33%) had skin type IV, others had skin type III (25%), skin type V (11.11%), and skin type II (5.56%)[5]. Treatment allocation and follow-up according to the Consolidated Standards of Reporting Trials (CONSORT) guidelines are illustrated in Figure 14.

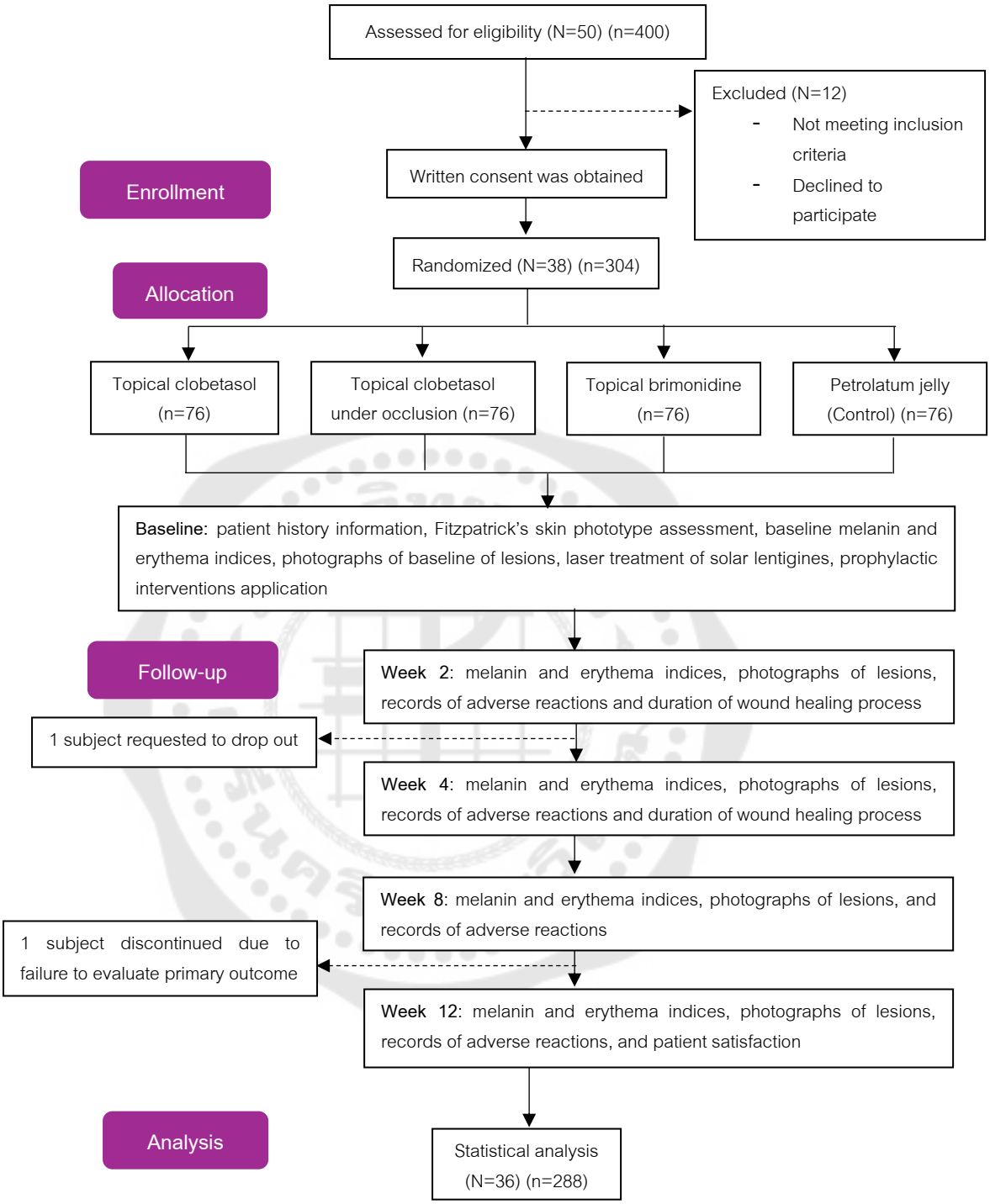


Figure 14 Flow chart of the study according to CONSORT guidelines; N=number of participants; n=number of lesions

Table 17 Baseline demographic characteristics

Characteristics	
Gender, N (%)	
Male	3 (8.33%)
Female	33 (91.67%)
Age (years), median (IQR)	58.5 (53.65)
Skin type, N (%)	
Type II	2 (5.56%)
Type III	9 (25.00%)
Type IV	21 (58.33%)
Type V	4 (11.11%)

N=number of patients (%)

Occurrence of PIH

The occurrence of PIH was assessed subjectively by dermatologists at week 2, 4, 8, and 12, as shown in Table 20. Total incidence of PIH in all of the lesions were 68.75% (198 out of 288 lesions). The accumulative incidence of PIH in topical clobetasol, topical clobetasol under occlusion, topical brimonidine, and control groups were 69.4%, 72.2%, 66.7%, and 66.7%, respectively. Linear mixed model was used to analyzed the overall incidence of PIH between all groups and no significance difference was found (p=702). Survival analysis showed that PIH most commonly occurred at week 4 and some lesions continued to develop PIH until 12 weeks after laser treatment. The hazard ratios (95% CI) between topical clobetasol, topical clobetasol under occlusion, and topical brimonidine groups, and the control group were 1.163 (0.78-1.73), 1.159 (0.78-1.72), and 1.029 (0.69-1.53), respectively. Although not statistically significant, a slight increase in the risk of PIH was observed in all intervention groups, compared with the control group[5]. Figure 15 and 16 show clinical photographs of representative cases that healed with and without PIH.

Table 18 Subjective assessment of occurrence of PIH determined by dermatologists at week 2, 4, 8, and 12

Visit	Group A (n = 72)	Group B (n = 72)	Group C (n = 72)	Control (n = 72)	Overall incidence (n = 288)	*p*-value
Week 2	5	3	4	3	15	
Week 4	34	31	26	23	114	
Week 8	7	16	13	20	56	
Week 12	4	2	5	2	13	
Accumulative incidence	50 (69.4%)	52 (72.2%)	48 (66.7%)	48 (66.7%)	198 (68.75%)	0.702
HR (95% CI)	1.163 (0.78-1.73)	1.159 (0.78-1.72)	1.029 (0.69-1.53)			

Values are number of lesions (%); Group A: topical clobetasol propionate 0.05% ointment twice daily for 2 days; Group B: single application of topical clobetasol propionate 0.05% ointment under occlusive dressings for 24 hours; Group C: topical brimonidine tartrate 0.33% gel 1 hour before and 3 days after laser treatment; Control: topical petrolatum jelly for 7 days; HR = Hazard ratio between the treatment and the control group; 95% CI = 95% confidence interval; *p*-value = comparison of accumulative incidence between all groups; Significance differences at $p < 0.05$.

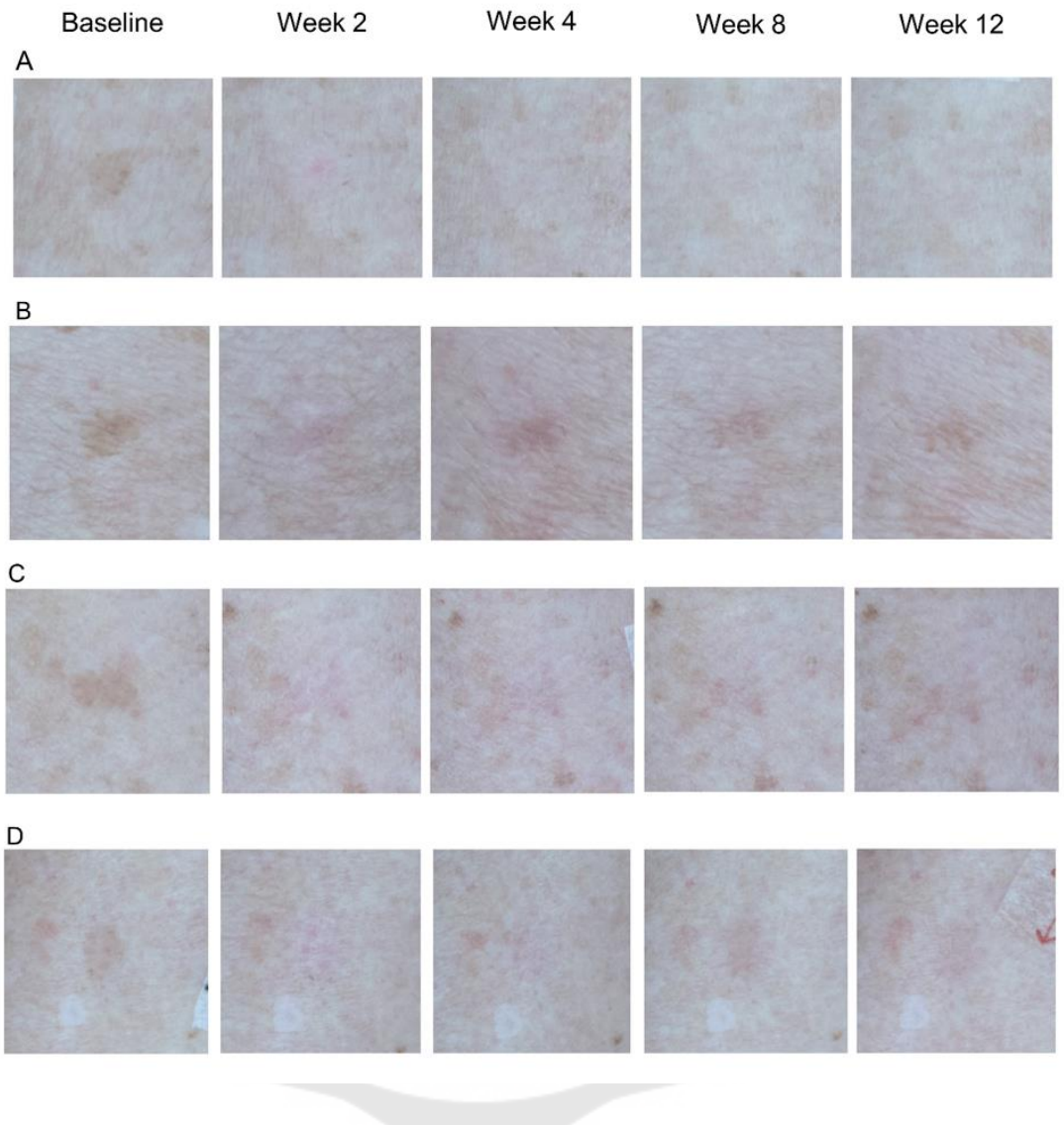


Figure 15 Clinical photographs after QS Nd:YAG 532-nm laser treatment with topical clobetasol propionate 0.05% ointment (A); topical clobetasol propionate 0.05% ointment under occlusive dressings (B); topical brimonidine tartrate 0.33% gel (C); topical petrolatum jelly (D, as PIH prophylaxis.

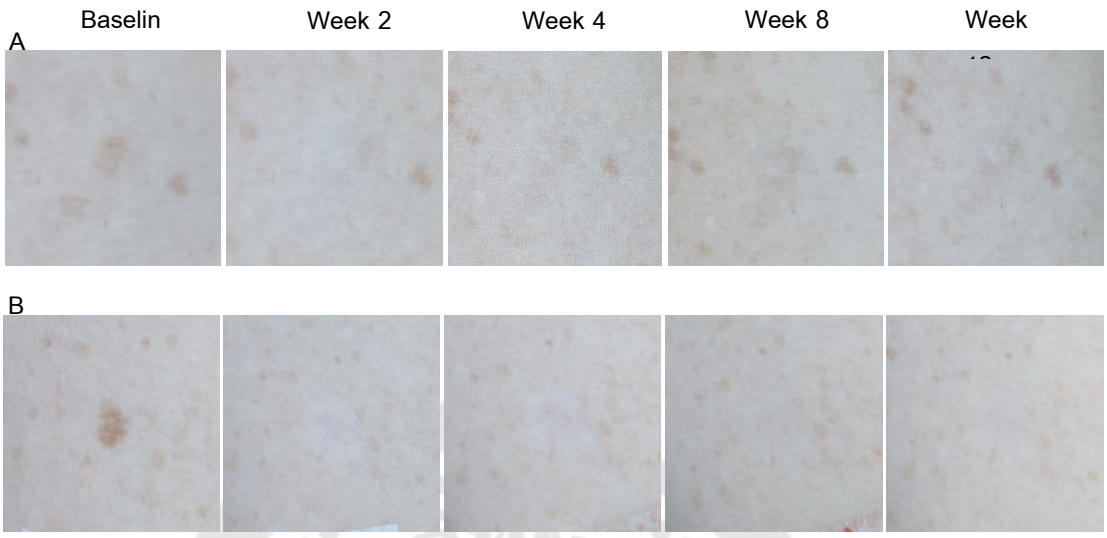
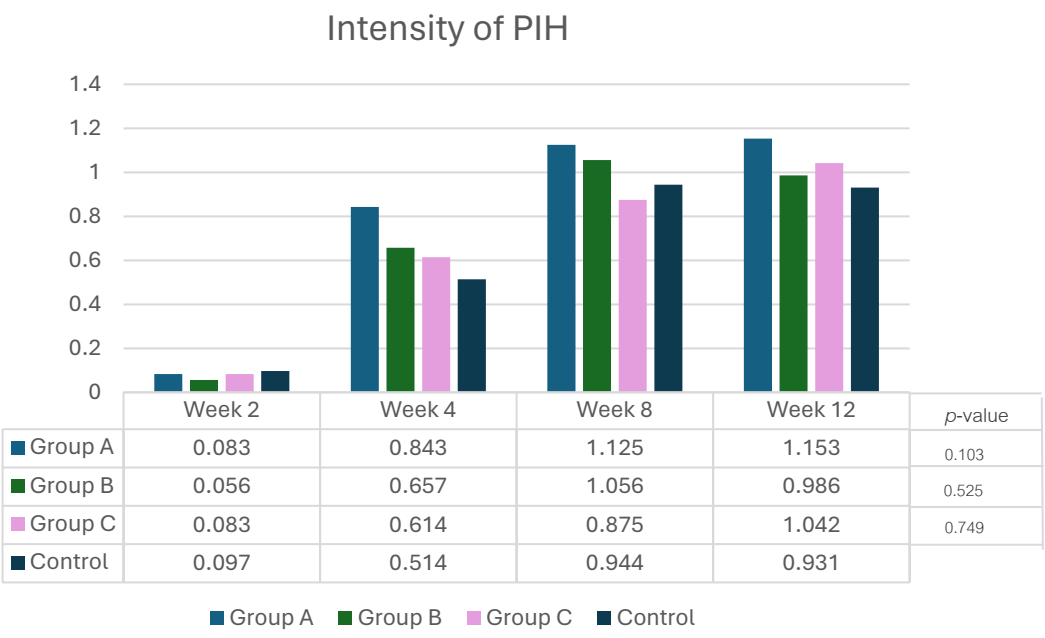


Figure 16 Example of lesions in the same patient that healed with PIH (A) and without PIH (B) at baseline, and week 2, 4, 8, and 12.

Intensity of PIH

In this study, the intensity of PIH was assessed subjectively using a 5-point grading scale, and objectively by measuring melanin index using Mexameter® MX 18, at week 2, 4, 8, and 12. Lesions in all groups exhibited comparable mean grading of PIH, as well as melanin index values, as presented in Figure 17. Topical clobetasol group was observed to have higher intensity of PIH at week 4, 8, and 12; however, this difference was not statistically significant. Overall, the intensity of PIH was not significantly different between the treatment and the control groups[5].

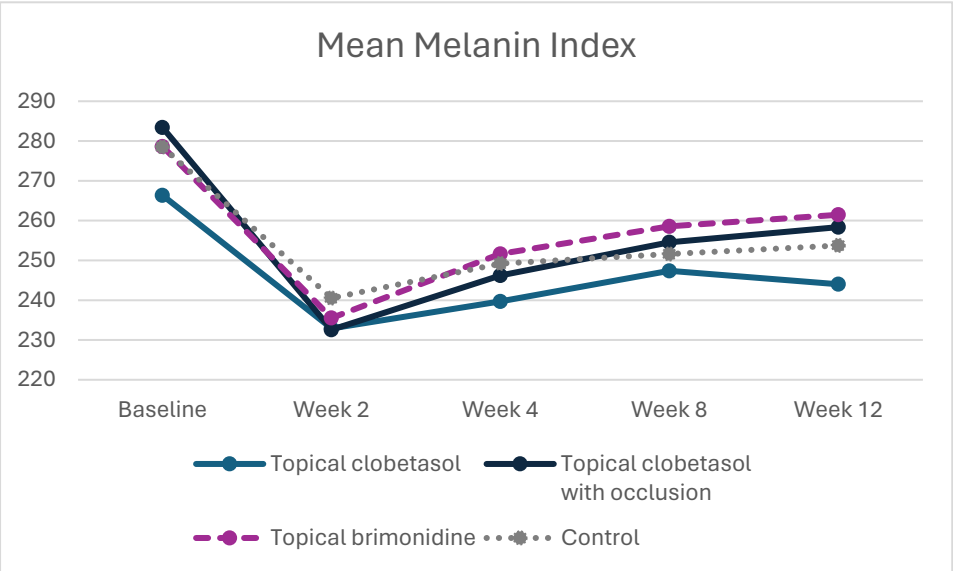
Moreover, there was no significant difference in melanin indices between Group A, B and C, compared to the control (*p*-value = 0.368, 0.941, 0.801, respectively) as illustrated in Figure 18. The baseline mean melanin indices (±SD) of Group A, B, C, and the control were 266.34 (±65.8), 283.40 (±63.4), 278.64 (±64.7), and 278.52 (±72.5), respectively, with no statistically significant difference between all groups. (p=0.611)[5].



	Week 2	Week 4	Week 8	Week 12	*p*-value
Group A	0.083	0.843	1.125	1.153	0.103
Group B	0.056	0.657	1.056	0.986	0.525
Group C	0.083	0.614	0.875	1.042	0.749
Control	0.097	0.514	0.944	0.931	

Group A: topical clobetasol propionate 0.05% ointment twice daily for 2 days; Group B: single application of topical clobetasol propionate 0.05% ointment under occlusive dressings for 24 hours; Group C: topical brimonidine tartrate 0.33% gel 1 hour before and 3 days after laser; Control: topical petrolatum jelly for 7 days; *p*-value = comparison of data between the intervention groups and the control group, calculated using linear mixed model; Significant difference at $p < 0.05$.

Figure 17 Intensity of PIH determined by the average grading of PIH for each intervention, at week 2, 4, 8, and 12



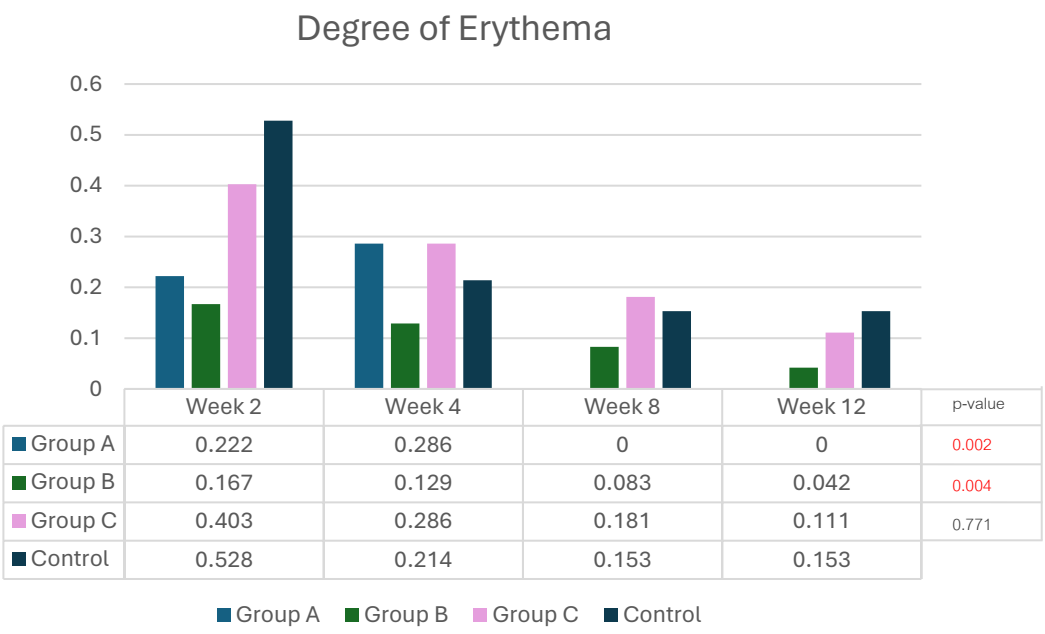
p-value

- Topical clobetasol vs Control: 0.368
- Topical clobetasol under occlusion vs Control: 0.941
- Topical brimonidine vs Control: 0.801

Figure 18 Mean melanin index at baseline, week 2, 4, 8, and 12 after treatment

Degree of Erythema

The subjective evaluation of the degree of erythema by dermatologists using a 5-point grading scale at week 2, 4, 8, and 12 is presented in Figure 19. Average grading of erythema was calculated and linear mixed model was used to statistically analyzed the difference of overall degree of erythema between the treatment and the control groups. In all of the intervention groups, mean grading of erythema decreased compared with the control, especially at week 2 after laser treatment. However, there was a significantly lower degree of erythema in the lesions that received topical clobetasol and topical clobetasol under occlusion than in the control group (*p*-values = 0.002 and 0.004, respectively)[5]. The difference of mean grading of erythema between topical brimonidine group and the control group was not statistically significant (p=0.771).

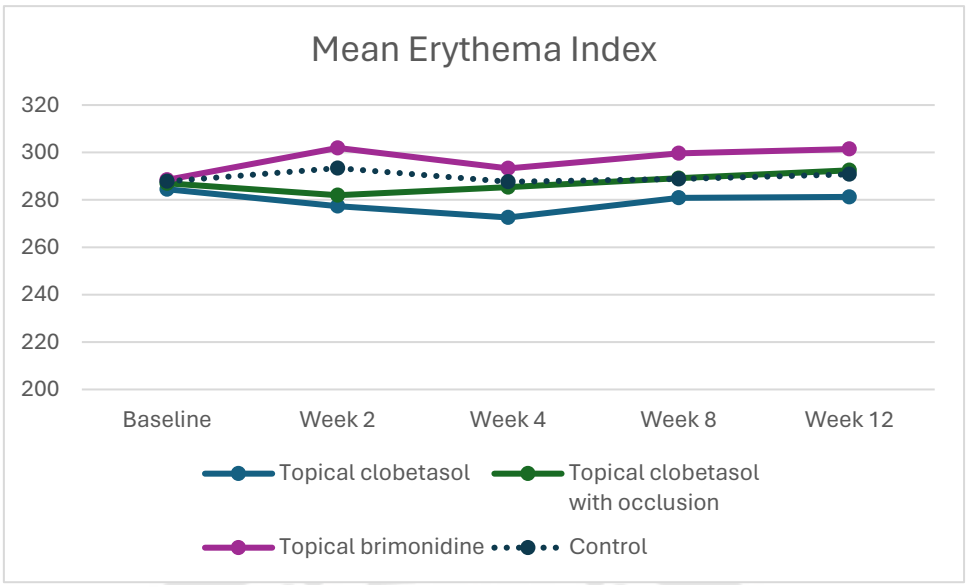


	Week 2	Week 4	Week 8	Week 12	p-value
Group A	0.222	0.286	0	0	0.002
Group B	0.167	0.129	0.083	0.042	0.004
Group C	0.403	0.286	0.181	0.111	0.771
Control	0.528	0.214	0.153	0.153	

Group A: topical clobetasol propionate 0.05% ointment twice daily for 2 days; Group B: single application of topical clobetasol propionate 0.05% ointment under occlusive dressings for 24 hours; Group C: topical brimonidine tartrate 0.33% gel 1 hour before and 3 days after laser; Control: topical petrolatum jelly for 7 days; *p*-value = comparison of data between the intervention groups and the control group, calculated using linear mixed model; Significant difference at $p < 0.05$.

Figure 19 Degree of erythema determined by average grading of erythema of each intervention at week 2, 4, 8, and 12

The objective measurement of erythema was performed using Mexameter® MX 18, at week 2, 4, 8, and 12. Mean erythema index of the lesions in each group was recorded and linear mixed model was used to analyzed the difference of the data between all groups. No significant difference regarding mean erythema index was found between group A, B, C and the control, as presented in Figure 20 (*p*-values = 0.311, 0.784, and 0.444, respectively).



p-value

- Topical clobetasol vs Control: 0.311
- Topical clobetasol under occlusion vs Control: 0.784
- Topical brimonidine vs Control: 0.444

Figure 20 Mean erythema index at baseline, week 2, 4, 8, and 12 after treatment

Improvement of lesions

The improvement of solar lentigo lesions was evaluated subjectively by dermatologists using a 5-point grading scale at week 2, 4, 8, and 12. It was measured on a scale of 0 to 4 (0, no change or worsening; 1, poor improvement 1-25%; 2, fair improvement 26-50%; 3, good improvement 51-75%; 4, excellent improvement 76-100%) and is presented in Figure 21. There was no significant difference regarding improvement of lesions between all groups throughout the study[5].

	Week 2	Week 4	Week 8	Week 12	*p*-value
Group A	2.06	2.84	2.52	2.4	0.565
Group B	2.54	3.34	2.69	2.63	0.180
Group C	2.54	2.88	2.63	2.44	0.735
Control	2.5	2.97	2.41	2.36	

Group A: topical clobetasol propionate 0.05% ointment twice daily for 2 days; Group B: single application of topical clobetasol propionate 0.05% ointment under occlusive dressings for 24 hours; Group C: topical brimonidine tartrate 0.33% gel 1 hour before and 3 days after laser; Control: topical petrolatum jelly for 7 days; *p*-value = comparison of data between the intervention groups and the control group, calculated using linear mixed model; Significant difference at $p < 0.05$.

Figure 21 Average grading of improvement of lesions of each intervention at week 2, 4, 8, and 12

Patient satisfaction

Patient satisfaction is presented in Table 21. In this study, a 5-point grading scale was used to evaluate various aspects of patient satisfaction. We grouped the data in grade 0 (very dissatisfied) and grade 1 (somewhat dissatisfied) into one category as 'dissatisfied'. In regard to the improvement of lesions, topical clobetasol under occlusion (Group B) showed significant improvement of lesions compared with that in the control group (p=0.042). Meanwhile, the lesions in Group A and C did not significantly improve, compared with the control (p=0.065 and 0.241, respectively). Satisfaction regarding convenience of use was significantly higher in all intervention groups, compared with the

control (p<0.001). The convenience of these approaches is likely due to less frequent application of topical medication compared to 7-day application of petrolatum jelly 4 times a day. Moreover, the sensation after application was significantly greater for all interventions (p<0.001 in Group A and B; p=0.001 in Group C compared to the control). The overall satisfaction of patients was significantly better in the topical clobetasol and topical clobetasol under occlusion groups than in the control group (p=0.028 and p=0.022, respectively)[5].

Table 19 Patient satisfaction

Satisfaction		Group A (n = 72)	Group B (n = 72)	Group C (n = 72)	Control (n = 72)	*p*-value
Improvement of lesions	Dissatisfied	0	0	2 (2.78%)	6 (8.33%)	0.020
	Neither dissatisfied nor satisfied	12 (16.67%)	8 (11.11%)	10 (13.89%)	12 (16.67%)	
	Satisfied	28 (38.89%)	40 (55.56%)	26 (36.11%)	30 (41.67%)	
	Very satisfied	32 (44.44%)	24 (33.33%)	34 (47.22%)	24 (33.33%)	
Convenience	Dissatisfied	0	0	0	0	<0.01
	Neither dissatisfied nor satisfied	6 (8.33%)	2 (2.78%)	6 (8.33%)	38 (52.87%)	
	Satisfied	12 (16.67%)	10 (13.89%)	38 (52.78%)	22 (30.56%)	
	Very satisfied	54 (75.00%)	60 (83.33%)	28 (38.89%)	12 (16.67%)	

Table 21 (continued)

Satisfaction		Group A (n = 72)	Group B (n = 72)	Group C (n = 72)	Control (n = 72)	*p*-value
Sensation after application	Dissatisfied	0	0	2 (2.78%)	0	<0.01
	Neither dissatisfied nor satisfied	4 (5.56%)	0	8 (11.11%)	28 (38.89%)	
	Satisfied	16 (22.22%)	18 (25.00%)	36 (50.00%)	28 (38.89%)	
	Very satisfied	52 (72.22%)	54 (75.00%)	26 (36.11%)	16 (22.22%)	
Overall satisfaction	Dissatisfied	0	0	0	0	<0.01
	Neither dissatisfied nor satisfied	8 (11.11%)	6 (8.33%)	10 (13.89%)	18 (25.00%)	
	Satisfied	24 (33.33%)	38 (52.78%)	24 (33.33%)	28 (38.89%)	
	Very satisfied	40 (55.56%)	28 (38.89%)	38 (52.78%)	26 (36.11%)	

Values are number of lesions (%); Group A: topical clobetasol propionate 0.05% ointment twice daily for 2 days; Group B: single application of topical clobetasol propionate 0.05% ointment under occlusive dressings for 24 hours; Group C: topical brimonidine tartrate 0.33% gel 1 hour before and 3 days after laser treatment; Control: topical petrolatum jelly for 7 days; *p*-value = comparison of data between all groups; Significance differences at $p < 0.05$.

Adverse reactions

Adverse reactions are listed in Table 22. Itching was significantly more prevalent in the lesions that received topical brimonidine, compared with other groups (p=0.001). 3 out of 72 lesions (4.17%) in the topical brimonidine group were reported to develop mild eczematous reactions which subsided within one week. The dryness of the lesions was not significantly different among all groups. There was no development of scarring or blistering. The potential side effects of topical corticosteroids, such as skin atrophy and acneiform eruptions, were also not detected throughout the study[5].

Table 20 Adverse reactions

Adverse reactions	Topical clobetasol	Topical clobetasol under occlusion	Topical brimonidine	Control	*p*-value
Itching	12 (16.67%)	8 (11.11%)	26 (36.11%)	12 (16.67%)	0.001
Dryness	18 (25.00%)	20 (27.28%)	22 (30.56%)	18 (25.00%)	0.872
Eczematous reactions	0	0	3 (4.17%)	0	0.061

Values are number of lesions (%); *p*-value = comparison of data between all groups; Significance differences at $p < 0.05$.

Duration of wound healing process

The mean duration of pain and edema was 1 day after laser therapy in all groups. The overall mean duration of crusting was 18.77±1.82 days and mean duration of erythema was 4.92±2.37 days. Moreover, there was no statistically significant difference regarding duration of wound healing process between all groups, as shown in table 23.

Table 21 Duration of wound healing process

Healing process	Topical clobetasol	Topical clobetasol under occlusion	Topical brimonidine	Control	P value
Pain, median (IQR)	1	1	1	1	>0.999
Crusting, mean (SD)	18.93 (1.76)	18.79 (1.75)	18.49 (1.83)	18.86 (1.94)	0.478
Edema, median (IQR)	1	1	1	1	>0.999
Erythema, median (IQR)	4 (3-7)	4 (3-7)	4.5 (3-7)	4.5 (3-7)	0.708

Values are number of days; *p*-value = comparison of data between all groups; Significance differences at $p < 0.05$.

CHAPTER 5
SUMMARY DISCUSSION AND SUGGESTION

Summary of findings

In this clinical trial, application of PIH prophylaxis regimens; including 2-day application of topical clobetasol propionate 0.05% ointment twice daily, single application of topical clobetasol propionate 0.05% ointment under occlusive dressings for 24 hours, and 1-hour pre-treatment and 3-day posttreatment application of topical brimonidine tartrate 0.33% gel once a day; did not significantly reduce the incidence of PIH following 532-nm Q-Switched Nd:YAG laser irradiation of solar lentigines on the forearms, compared with 7-day application of petrolatum jelly four times a day as control (p=0.702).

Moreover, the mean grading of intensity of PIH were not significantly different between topical clobetasol, topical clobetasol under occlusion, topical brimonidine, and the control groups (p=0.103, 0.525, 0.749, respectively). Correspondingly, the difference in mean melanin index values between all of the intervention groups and the control group were also not statistically significant (p=0.368, 0.941, 0.801, respectively).

In regard to the degree of erythema, significantly lower mean grading of degree of erythema was demonstrated in the lesions that received topical clobetasol and topical clobetasol under occlusion, compared to those applied with petrolatum jelly (p=0.002, 0.004, respectively). Topical brimonidine, on the other hand, did not significantly reduce posttreatment erythema, compared with the control (p=0.771). There was also no significant difference regarding mean erythema index values between topical clobetasol, topical clobetasol under occlusion, topical brimonidine, and the control groups (p=0.311, 0.784, and 0.444, respectively).

Furthermore, when evaluated by dermatologists, the improvement of lesions in topical clobetasol, topical clobetasol under occlusion, and topical brimonidine groups, were comparable with the control group (p=0.565, 0.180, 0.735). However, patient satisfaction regarding improvement of lesions were significantly higher in topical clobetasol under occlusion group, compared with the control (p=0.042). Satisfaction

regarding convenience of the application and sensation after applying were also significantly greater among all intervention groups than the control group ($p<0.001$). Overall satisfaction was reported to be highest in topical clobetasol group, followed by topical clobetasol under occlusion group, which was significantly higher than the control ($p=0.028$, 0.022, respectively).

In addition, the lesions that received topical brimonidine significantly developed more itching symptom than other groups ($p=0.001$). Eczematous reactions also developed in 3 lesions in the group. The duration of wound healing process in all groups was not significantly different.

Discussion

PIH is one of the most frequent complications that can occur after receiving dermatologic procedures, including laser therapy. The condition can arise in all skin types but tends to affect patients with Fitzpatrick skin phototypes (SPTs) III to VI[11]. The development of PIH is associated with several factors, including the skin type of the patients, sun-exposure before laser treatment, the damage of the dermal–epidermal junction, and the degree of inflammation at the basement membrane[5, 27].

PIH results from an increase in melanin production or an abnormal distribution of melanin to surrounding keratinocytes after skin damage or inflammation. This reaction can be generated by nonspecific thermal damage that occurs during laser therapy. Although the precise mechanism has not been fully explored, the increase in melanocyte activities, including melanin synthesis and melanin transfer, is thought to be stimulated by reactive oxygen species that are generated during the process of inflammation, and also stimulated by inflammatory mediators such as prostanoids, cytokines, and chemokines[11]. The melanocyte-stimulating function of these mediators has been demonstrated in several studies[12, 13]. In addition, PIH can occur as a result of pigmentary incontinence; damage to the basal keratinocytes leads to a release of melanin to be phagocytosed by melanophages in the papillary dermis, which results in dermal hyperpigmentation on the affected skin[5, 14, 15].

Topical corticosteroids may potentially prevent PIH through the inhibition of phospholipase A2 and suppressing the release of platelet activating factors and arachidonic acid from the cell membrane; consequently, the release of inflammatory mediators, including leukotrienes and prostaglandins, is interrupted. They further lead to the inhibition of melanogenesis[13]. Cheyasak et al. conducted a study using topical clobetasol propionate 0.05% ointment in the prevention of PIH after ablative fractional CO_2 laser resurfacing in 40 Asians with atrophic acne scars and SPTs IV. One side of the face was treated with clobetasol propionate twice a day for 2 days, while the other side was treated with petrolatum jelly 4 times per day. A significantly higher incidence of PIH was found on the side treated with petrolatum jelly (75%), compared with the side treated with topical clobetasol (40%)[5, 19].

Despite the aforementioned supporting evidence; our study demonstrated that topical clobetasol, along with topical clobetasol under occlusion, and topical brimonidine, did not significantly reduce the occurrence of PIH after laser treatment of solar lentigines, compared with the control. Moreover, the intensity of PIH tended to increase at 8 and 12 weeks after treatment. According to a previous study which electron microscope was used to demonstrate that inflammation in the skin can persist for 20 days following Q-switched irradiation; we hypothesize that, in our study, the process of PIH development might continue during this period after the application of PIH prophylactic treatment[129]. Therefore, longer duration of prophylactic regimen might be needed in order to reduce the occurrence of PIH following Q-switched laser treatment of solar lentigines[5].

Moreover, in a previous study, 2-day application of topical clobetasol after treatment was shown to be effective in reducing the incidence of PIH following fractional CO_2 laser resurfacing in patients with SPTs IV[19]. However, our study demonstrated that topical clobetasol, along with topical clobetasol under occlusion and topical brimonidine, did not significantly reduce the occurrence of PIH, compared with control. This may result from the difference in laser-tissue interactions between both laser treatments. The 532-nm Q-switched Nd:YAG laser operates based on the principle of selective photothermolysis and generates short burst, high-intensity radiation, which results in

thermal and mechanical effects that lead to the rupture of melanosomes and other melanin-containing cells. Subsequently, the fragmented pigments are phagocytosed by macrophages, which later become melanophages, leading to gradual clearance of the pigment[130]. A previous study in which tissue biopsies were obtained immediately following the treatment of solar lentigines with Q-switched laser showed destruction of melanosomes in clusters with visible damage to the basement membrane[131]. We hypothesize that this might result in larger amount of melanin released from keratinocytes and melanocytes following Q-switched laser irradiation, thus more hyperpigmentation occurred due to pigmentary incontinence, which may not be very responsive to topical corticosteroids, and can possibly cause delayed PIH more than ablative laser therapy. It is also possible that for pigmented laser treatment, a longer duration of prophylactic regimen might be needed in order to reduce the occurrence of PIH after treatment[5].

Topical brimonidine gel can cause potent vasoconstrictive effect on dermal blood vessels with a diameter of less than 200 μm. The mechanisms by which topical brimonidine reduces PIH after laser treatment is not clearly understood. Previous studies in patients with solar lentigo and melasma suggested that an increased blood flow and vascularity may be associated with pigmentation[25, 26]. Therefore, reducing blood flow through the vasoconstrictive effect of topical brimonidine maybe another preventive measure for PIH. However, in this randomized controlled trial, topical brimonidine did not reduce the incidence or intensity of PIH, or the degree of erythema after treatment with the QS laser. Furthermore, there was a dissatisfaction regarding sensation after applying topical brimonidine which correlated with the adverse effects of itching (36.11%), dryness (30.56%), and eczema (4.17%) which are most common in topical brimonidine group. According to the results of this study, topical brimonidine should not be used for PIH prevention following laser treatment due to the risks that outweigh the benefits[5].

The overall incidence of PIH in this study was 68.75%, which is higher than previous studies demonstrating 8.47-47% of PIH incidence following Q-switched laser treatment of solar lentigines[4, 6-11]. This might be attributable to the use of laser irradiation with an endpoint of obvious immediate whitening within the lesions. Negishi et al. found

that solar lentigines that received Q-switched laser treatment with an endpoint of obvious immediate whitening had higher risk of PIH development compared with the lesions that achieved an endpoint of slightly immediate whitening[6]. Additionally, some patients admitted that they did not strictly avoid sun exposure or had adequate sun protection after the treatment due to their life styles or their occupations. This could also affect the incidence of PIH as demonstrated by a previous study that suntan can increase the risk of PIH among patients that received laser irradiation[132]. Moreover, most of the previous studies performed the treatment in facial area, while in our study, the treatment was performed on the forearms. This is consistent with a previous study of Chinese patients who underwent fractional resurfacing using a 1540-nm Erbium glass laser. Significantly higher incidence of PIH was reported in the forearm area, compared with facial area. This might be a result of the lower density of sebaceous follicular unit in the forearm area[72]. Further study is needed to reveal the association between different body sites and the development of PIH after laser therapy. To minimize the incidence of PIH after laser procedures, there might be several other factors that should be considered; for example, primary diagnosis, skin type of the patients, sun exposure, past history of PIH and laser parameters[5, 16].

Meanwhile, topical clobetasol and topical clobetasol under occlusion were observed to be effective in reducing overall post-treatment erythema, compared with the control group. This could result from the anti-inflammatory and the vasoconstrictive effects of the treatment. However, in the present study, the application of topical brimonidine, which has potent vasoconstrictive effect, before and after QS laser, did not reduce posttreatment erythema. Furthermore, compared with the control treatment, topical brimonidine group exhibited increased erythema at week 4 and 8. This finding demonstrated that the vasoconstriction property of topical brimonidine may not be sufficient in order to prevent posttreatment erythema and PIH, which multiple factors are involved in the pathogenesis[5].

Interestingly, overall patient satisfaction was highest in the lesions that received topical clobetasol and topical clobetasol under occlusion. This could be due to the sensation after application and the convenience of use. In addition, lesions that received topical clobetasol under occlusion achieved the highest satisfaction scores regarding convenience and sensation. This is likely due to ease of use and the soothing effect of film dressing. Moreover, short-term application of topical clobetasol did not increase adverse effects compared to application of petrolatum jelly. This approach may be applied in clinical practice as a favorable post-laser protocol in order to improve patient satisfaction and convenience after treatment[5].

Table 22 Comparison between previous studies and this study

	Uaboonkul et al.[110]	Cheyasak et al.[19]	This study[5]
Year of study	2012	2015	2023
Study design	RCT, split-face	RCT, split-face	RCT, intra-individual comparison
Number of participants (n)	25	40	36
Age of participants	18-60 years	≥18 years	≥18 years
Primary lesion	Facial Hori nevus	Facial atrophic acne scars	Solar lentigines on the forearms
Fitzpatrick's skin phototypes	N/A	IV	II-V
Laser irradiation	Q-Switched Nd:YAG 1064-nm laser	Fractional CO_2 laser resurfacing	Q-Switched Nd:YAG 532-nm laser

Table 23 (continued)

	Uaboonkul et al.	Cheyasak et al.	This study
Year of study	2012	2015	2023
Duration of study	8 weeks	12 weeks	12 weeks
Intervention	Fusidic acid combined with betamethasone valerate cream (Fucicort cream®) applied twice a day for 2 weeks	Topical clobetasol propionate 0.05% ointment applied twice a day for the first 2 days	**Group A**: Topical clobetasol propionate 0.05% ointment applied twice daily for 2 days **Group B**: Topical clobetasol propionate 0.05% ointment applied once under occlusive dressings for 24 hours **Group C**: Topical brimonidine tartrate 0.33% gel applied 1 hour pre-treatment then once a day for 3 days posttreatment
Control	Fusidic acid (Fucidin cream®) applied twice a day for 2 weeks	Petrolatum jelly applied four times a day for 7 days	Petrolatum jelly applied four times a day for 7 days
Outcome measurement	Melanin index and erythema index measured using Mexameter® MX18. Photographic assessment of degrees of PIH by dermatologists.	Occurrence and severity of PIH determined clinically by a dermatologist, Improvement of acne scars determined from digital photographs	Occurrence of PIH, intensity of PIH, degree of erythema, improvement of lesions, determined by dermatologists. Melanin index and erythema index measured using Mexameter® MX18.

Table 24 (continued)

	Uaboonkul et al.	Cheyasak et al.	This study
Year of study	2012	2015	2023
Results	- Melanin index did not significantly differ between both sides of the face - The control side showed increased PIH by 2nd week post-laser, and cumulative increase in pigmentation at the 4th and 8th weeks (not statistically significant) - Erythema indices of the tested sides were lower than the control side (not statistically significant)	- The control side had significantly higher incidence of PIH posttreatment and significantly higher PIH intensity/surface area - No significant difference in acne scar improvement between both sides of the face	- Occurrence and intensity of PIH, as well as melanin index values, were not statistically different between the lesions in all groups - Degree of erythema was significantly lower in the topical clobetasol and topical clobetasol groups - Improvement of solar lentigo lesions were not significantly difference between all groups

Strength of this study

This study has multiple advantages. There were large number of lesions in the study, with a total of 288 lesions, each group containing 72 lesions. Furthermore, the lesions were divided into 3 intervention groups and a control group, which allows for the experiment of various evidence-based PIH prophylaxis regimens. The duration of study was 12 weeks, therefore, delayed PIH could be detected and trend of change regarding the intensity of PIH could be observed.

Study limitations

This current study has several limitations. The location of solar lentigo (epidermal pigmentation) on the forearm may not represent the incidence of PIH in other areas, such as the face and other types of pigmented lesions. Secondly, many patients were not able to avoid sun exposure for 12 weeks. However, this situation also commonly occurs in the clinical practice, therefore, this might be considered to be similar to the real-world settings[5].

Conclusion

In conclusion, in this clinical trial, topical clobetasol, topical clobetasol under occlusion, and topical brimonidine were not found to be significantly effective in reducing the incidence and intensity of PIH after laser treatment of solar lentigines on the forearms. However, patient satisfaction, as well as the reduction in posttreatment erythema after laser treatment, were significantly greater in lesions that received topical clobetasol and clobetasol under occlusion. None of the interventions showed benefit over petroleum jelly in terms of improvement of lesions and wound healing. In addition, adverse reactions were most frequently reported in the topical brimonidine group[5].

Suggestions

Despite the widely use of topical clobetasol for PIH prophylaxis in clinical practice, there is currently limited supporting evidence to demonstrate the efficacy of the treatment. Adverse reactions can also occur; therefore, we still suggest that these interventions should be applied only in selected patients. Further study using longer duration of prophylactic treatment is needed to determine the effectiveness, along with the risks and benefits, of topical clobetasol, topical clobetasol under occlusion, and topical brimonidine in the prevention of post-inflammatory hyperpigmentation after laser treatment of solar lentigines[5].

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Appendix

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This research study has been submitted for consideration of publication and is currently under revision at Archives of Dermatological Research. Therefore, the high similarity score on Turnitin for this thesis reflects the matching of content to the preprint of this study in the databases.

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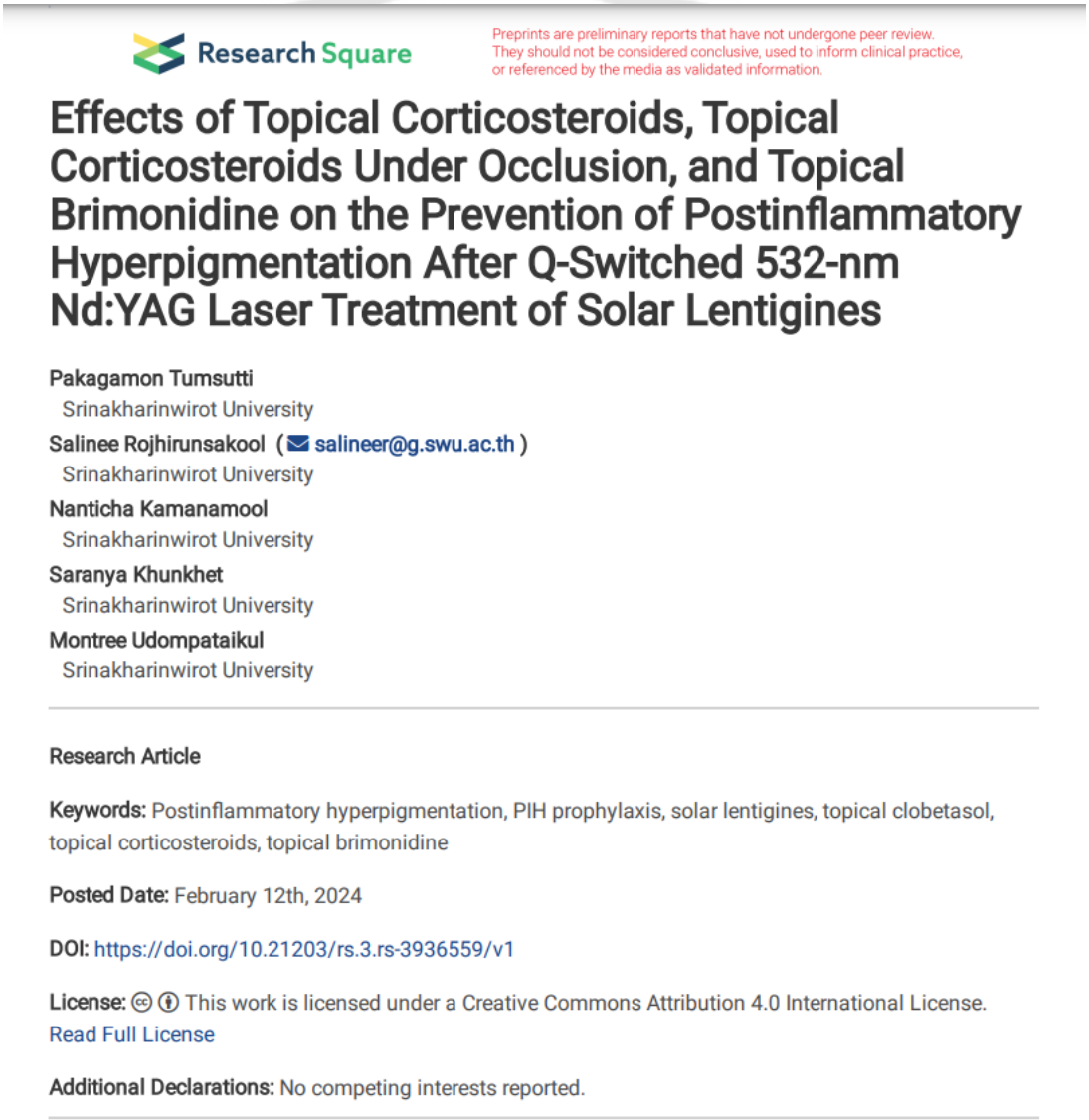

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Effects of Topical Corticosteroids, Topical Corticosteroids Under Occlusion, and Topical Brimonidine on the Prevention of Postinflammatory Hyperpigmentation After Q-Switched 532-nm Nd:YAG Laser Treatment of Solar Lentigines

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