CLINICAL REPORT

Topical Corticosteroids Minimise the Risk of Postinflammatory Hyperpigmentation After Ablative Fractional CO₂ Laser Resurfacing in Asians

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Postinflammatory hyperpigmentation (PIH) is the most common adverse effect of laser treatment in dark-skinned individuals. Little is known whether PIH can be prevented or minimised. The objective of this study was to investigate the effect of short-term application of topical corticosteroids on the incidence of PIH after ablative fractional resurfacing in Asians. Forty subjects with skin phototype IV and atrophic acne scars were treated with a fractional CO₂ laser on both sides of the face. Post-operatively, clobetasol propionate 0.05% ointment was applied to one randomly selected side of the face for the first 2 days, followed by an application of petrolatum jelly for the rest of the week (petrolatum was applied to the other side for 7 days). Assessments on the clinical outcome, the wound healing process and the occurrence of PIH were obtained once weekly for the first month and at 2 and 3 months post-treatment. The side of the face treated with petrolatum alone had significantly ($p<0.001$) higher incidence of PIH (75%) after laser irradiation than the side of the face treated with topical corticosteroids and petrolatum (40%). The PIH occurring on the petrolatum-treated sides had significantly higher intensity ($p<0.001$) and was spread over a significantly larger area ($p<0.001$), compared with the corticosteroid- and petrolatum-treated sides. In conclusion, a short-term application of topical corticosteroids postoperatively is associated with a decreased risk of PIH after ablative fractional resurfacing. *Key words: corticosteroids; postinflammatory hyperpigmetation; laser resurfacing.*

Postinflammatory hyperpigmentation (PIH) is an acquired hypermelanosis occurring as a consequence of cutaneous inflammation from a wide range of aetiologies including inflammatory dermatoses, infections, allergic reactions, mechanical injuries, reactions to medications and therapeutic procedures (1). The pathogenesis of PIH includes an increase in melanin production and an abnormal distribution of this pigment. PIH tends to affect darker skinned patients including African Americans, Hispanics/Latinos, Asians, Native Americans, Pacific Islanders, and those of Middle Eastern descent with greater frequency and severity. Although PIH is not life threatening and mostly not permanent, it may cause considerable psychological stress and lower self-esteem with affected individuals. Treatment of PIH is difficult because there are few, if any, therapeutic options that are consistently successful. Little is known about whether PIH can be prevented or minimised (2).

Ablative fractional resurfacing (AFR) using carbon dioxide (CO₂) (3, 4), erbium-doped yttrium aluminum garnet (Er:YAG) (5, 6), and erbium-doped yttrium scandium gallium garnet (7) has been proven effective for treatment of atrophic scars. However, transient PIH is the most common adverse effect after AFR, especially in dark-pigmented individuals. Incidence of PIH following AFR in patients with skin phototype (SPT) IV is as high as 92% (4), whereas an incidence of 1.2% observed in patients with SPTs I–II using a similar type of ablative fractional CO₂ laser (8).

The development of PIH depends on a number of factors, including the patient's SPT, the presence of a suntan before laser therapy, the degree of disruption of the dermal–epidermal junction, and the degree of inflammation at the dermal-epidermal junction (9). Previous data suggested that arachidonic acid metabolites such as prostaglandin (PG) E₂, leukotrienes (LT) C₄ and thromboxanes (TX) B₂ may be responsible for the induction of PIH (10). These arachidonate-derived chemical mediators were produced from components of cell membranes at inflammatory sites and were demonstrated to have a stimulatory effect on human melanocyte by accelerating melanin production and melanosome transferring process (11).

A previous study demonstrated that the degree of UVB-induced erythema and hyperpigmentation were reduced in parallel manner by applying topical corticosteroids immediately after UVB irradiation (12). This observation has led us to speculate that anti-inflammatory properties of topical corticosteroids may have beneficial effects in minimising the risk of PIH occurring after laser irradiation.

MATERIAL AND METHODS

Patients

Forty subjects aged ≥18 years with atrophic facial acne scars for at least 6 months before entering the study were recruited to this split-face, single-blind comparison trial. The study protocol and informed consent documents were submitted and approved by our institutional review board. All participants were given verbal and written information about the study and gave signed informed consent before enrollment. Patients who were pregnant or lactating, who smoked, who had skin infections or inflamed acne or photosensitive dermatoses, who had concomitant treatment to the involved skin areas or had a propensity for keloid scarring, or who received isotretinoin or underwent filler injections or ablative/nonablative laser skin resurfacing procedures within the preceding 3 months were excluded from the study.

Treatment

All patients were treated with a fractional CO_2 laser (AcuPulse; Lumenis, Santa Clara, CA) by a single physician (NC). Preoperatively, lidocaine 2.5% and prilocaine 2.5% cream (a eutectic mixture of local anaesthetic, AstraZeneca LP, Wilmington, DE, USA) was applied under occlusion for an hour. Both sides of each individual subject's face were treated with a single pass of fractional CO_2 laser using the same treatment parameters. The laser was operated at a fixed pulse duration of 950 μs, and an average energy of 12.75 mJ (range 10–15 mJ) with an average of 5% skin surface coverage. No concurrent use of an epidermal cooling device was performed during the procedure. These treatment parameters are commonly used and found to be safe and effective in our current practice for facial skin resurfacing in Asian patients of skin phototype IV–V.

Immediately after the irradiation, there was a distinct stippled whitish fractional epidermolysis pattern that aided in visualisation of the treatment progress. The thin layer of superficial crusting was not removed because this served as a biocompatible wound dressing. No postoperative analgesic treatment was required beyond the application of ice compresses for approximately 15–20 min. No prophylactic antibiotics or antivirals were given to any patient.

Postoperative care

Subjects were instructed to cleanse the treated sites gently with tap water postoperatively. Two sides of each patient's face were randomly treated with 2 different post-treatment care regimens; one side of the face was applied clobetasol propionate 0.05% ointment (Dermovate®, GlaxoSmithKline UK, Middlesex, United Kingdom) twice daily for the first 2 days, followed by petrolatum jelly alone 4 times a day for the rest of the week, and the other side was applied petrolatum jelly alone 4 times a day for 7 days. Subjects were instructed to use 2 separated cotton-tipped applicators for applying clobetasol propionate ointment and petrolatum jelly in order to avoid the contamination. The randomisation list was generated with the web-based toll random.org (http://www.random.org/lists/).

After the crusting completely healed, all subjects were instructed to wear a broad-spectrum sunscreen with a sun protection factor of 50, avoid sun exposure, and avoid the use of any topical preparations on the face for the period of the study.

Subjective evaluation

All study participants were physically examined for the occurrence of PIH on the treatment areas by a board-certified dermatologist (WM), once weekly for the first month and at 2 and 3 months postoperatively. The severity of PIH was also rated according to its degree of intensity (none: no PIH; minimal: 1–25% darkening; mild: 26–50%; moderate: 51–75%; and severe: 76–100%) and extent (none: no PIH; minimal: involving <25% of the treated area; mild: 26–50%; moderate: 51–75%; and widespread: 76–100%).

Photographic documentation using identical camera settings, lighting, and patient positioning were obtained at baseline, once weekly for the first month and at 2 and 3 months post-treatment. All digital photographs were performed with a facial photo fixture using a Canon PowerShot G10 stand-off camera (OMNIA ImagingSystem, Canfield Scientific, Inc, Fairfield, NJ). The system consists of a configurable head support that ensures the proper and consistent registration of the position of the patient's head. The fixture ensured a fixed distance and fixed angle between the patient and the camera. The imaging station provides preset camera angles for frontal through full profile together with the MatchPose image overlay for quick and accurate patient positioning. Flash lamps placed in fixed positions to the camera ensured even illumination of all parts of the face and the ability to examine subjects under controlled lighting. Two blinded, medical assessors (RW and PM) independently assessed clinical improvement in the appearance of acne scars shown in comparable, standardised digital photographs using a quartile grading scale (0: <25%; 1: 25–50%; 2: 51–75%; 3: >75% improvement) after the treatments at 1- and 3-month follow-up visits.

Assessments by patients on the duration of pain after treatment and wound recovery process (duration of crusting, erythema and oedema), and other adverse effects were recorded at each follow-up visit. Immediately after fractional CO_2 resurfacing, study subjects were also asked to rate the pain associated with treatment using a 10-point pain scale (0: no pain to 10: severe pain).

Objective evaluation

Designated areas of scars on both sides of the face were marked on every subject and mapped with a translucent sheet during the first visit to ensure the consistency of the scar location. The degree of skin pigmentation and erythema of selected areas of scars was measured by Mexameter MX18 (Courage-Khazaka electronic GmbH, Cologne, Germany). Scar volume of designated scars of each individual subject was objectively evaluated by using an ultraviolet A-light video camera (VisioscanVC 98, Courage-Khazaka, Köln, Germany) with analysis software (Surface Evaluation of the Living Skin, Courage-Khazaka). Both devices consist of a handheld probe that makes contact at designated areas. An average value of 2 measurements on a representative scar on each side of the face was obtained. The evaluation was done at baseline and 1, 2, 3, 4, 8 and 12 weeks after the laser treatment.

Statistical analysis

The Wilcoxon signed rank test was used to determine if there was any significant difference in the clinical change scores by comparing the clinical photographs at baseline and at 12-week follow-up visits. The PIH incidence was calculated out of the total number of each postoperative regimen and the Chi-Square test was used to compare the risk of PIH between the 2 post-treatment regimens.

Analyses of repeated measures, including repeated measures analysis of variance and multivariate analysis were performed to test the differences in the means of scar pigmentation and erythema measured with the Mexameter (baseline, 1, 2, 3, 4 and 8 weeks after laser treatment) and scar volume measured with a UVA-light video camera (baseline and 3 months after laser treatment). The statistical tests were two-sided, and a probability value of less than 5% was considered statistically significant.

RESULTS

Forty subjects (21 females, 19 males) enrolled completed the protocol and were followed through the end of the study. All of them were skin phototype IV. The mean age of acne scars was 98 months (ranged from 6–360 months).

The side treated with petrolatum alone had a significantly ($p < 0.001$) higher incidence of PIH (PIH incidence of 75%) following laser irradiation than the side treated with topical clobetasol and petrolatum jelly (PIH incidence of 40%). The clinical evaluation corresponded to the pigmentation and erythema measurements (Fig. 1). Comparing with the petrolatum-treated side, the clobetasol and petrolatum-treated side had significantly lower intensity ($p < 0.001$) and spread over a significantly smaller area ($p < 0.001$). The intensity of PIH was mostly rated as minimal in 30% (12/40) and 37.5% (15/40) of patients with clobetasol and petrolatum-treatment, and only petrolatum-treatment, respectively (Table I). The extent of PIH was mostly graded as mild in 25% (10/40) and 37.5% (15/40) of patients on clobetasol and petrolatum-treated side, and petrolatum-treated side, respectively (Table I). Figs S1 and S2[1] demonstrate an occurrence of PIH on the petrolatum jelly-treated side only in 2 representative patients. In addition, the petrolatum jelly-treated sides were associated with longer duration of postoperative discomfort ($p = 0.004$), crusting ($p = 0.035$) and oedema ($p = 0.017$). There were no significant differences in duration of erythema ($p = 0.089$), and other adverse effects between 2 postoperative regimens (Table II).

There was no statistically significant difference in scar improvement between the 2 sides of the face ($p = 0.54$). At 3 months after one treatment, 25% of the petrolatum jelly-treated and clobetasol plus petrolatum-treated sides were assessed to have more than 50% improvement of the scar appearance. At

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Table. I. *Postinflammatory hyperpigmentation (PIH) intensity and extent in 40 patients undergoing laser resurfacing*

PIH	Clobetasol + petrolatum n	Petrolatum only n
Intensity		
Severe	0	0
Moderate	0	0
Mild	4	15
Minimal	12	15
None	24	10
Extent		
Severe	0	0
Moderate	0	3
Mild	10	15
Minimal	6	12
None	24	10

3-month follow-up visit, Visioscan analysis also did not demonstrate statistically significant difference in skin surface smoothness ($p = 0.92$) and scar volume ($p = 0.58$) between the petrolatum alone and clobetasol plus petrolatum sides.

Adverse effects

Of 40 subjects treated, 3 (7.5%) developed acneiform eruption on the third and fourth day postoperatively. Two of these eruptions were on the side treated with corticosteroids and petrolatum jelly and one eruption developed on the side treated with petrolatum jelly only. Gram stains and bacterial cultures were performed and revealed no growth of microorganisms. The eruption was successfully treated with clindamycin 1% solution and adapalene 0.1% gel. No other adverse effects such as scarring or herpes simplex infection were observed.

DISCUSSION

PIH remains the most common hindrance of cutaneous laser therapy in patients with dark-skinned complexions. The almost universal appearance of transient PIH
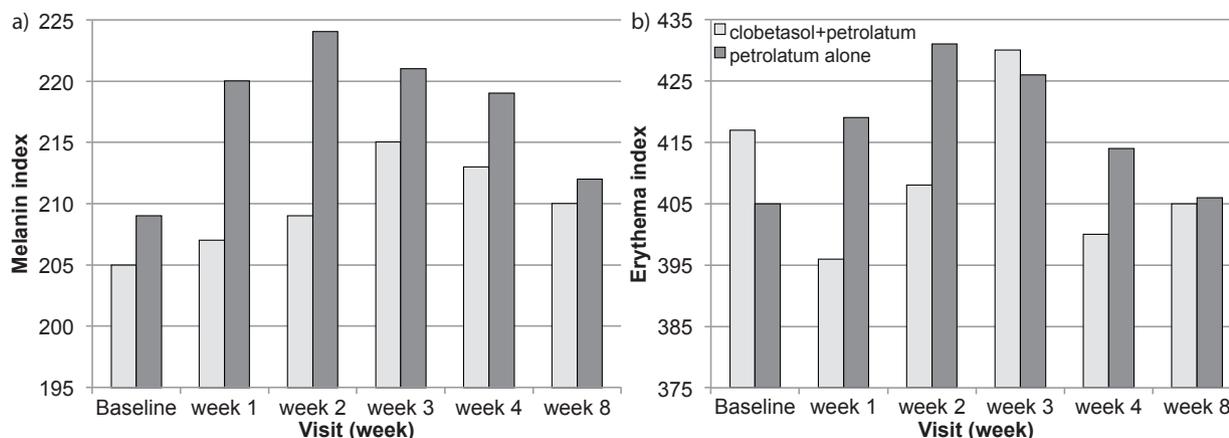

Fig. 1. Mean of melanin (a) and erythema (b) index of designated areas of the scars.

Table II. *Wound recovery process assessed by study subjects*

	Clobetasol + petrolatun Mean ± SD	Petrolatum only Mean ± SD	*p*-value
Pain, hour	11.4 ± 12.1	15.6 ± 19.2	0.004
Crusting, day	6.1 ± 2.9	6.5 ± 2.9	0.035
Erythema, day	4.5 ± 3.9	4.8 ± 3.4	0.089
Oedema, day	1.7 ± 1.1	2.0 ± 1.3	0.017

necessitates prompt and persistent intervention. Treatment of PIH is often difficult and prolonged, requiring a great deal of patience and therapeutic modalities to achieve a successful outcome. Once PIH occurs, it lasts 3–4 months on average, but it may persist as long as a year (4). Preoperative treatment with topical hydroquinone, tretinoin, glycolic acid, and vitamin C has been found to be ineffective in decreasing the incidence of PIH (13, 14). In contrast, these topical preparations can be helpful in treating PIH (13).

Pathogenesis of PIH has been postulated as a biologic response of keratinocytes and/or melanocytes to the inflammatory phase of the wound-healing cascade and this type of environment can be induced by nonspecific thermal damage caused during laser irradiation. There is an overproduction of melanin and an irregular dispersion of pigment after cutaneous inflammation (15). In the epidermis, over-produced melanin is transferred to the surrounding keratinocytes. An increase in melanocyte activity has been proposed to be stimulated by prostanoids, cytokines, chemokines, and other inflammatory mediators as well as reactive oxygen species that are released during the inflammatory process. In general, treatment of PIH should be initiated early to hasten its resolution, starting from management of the initial inflammatory process (2). Based on the aforementioned PIH pathogenesis, we demonstrated that short-term application of topical corticosteroids starting immediately after ablative fractional CO_2 laser resurfacing significantly reduced the risk of PIH. The use of topical corticosteroids in the present study may play a major role in lessening an inflammatory reaction during the wound-healing cascade, thus minimising the melanocyte activity.

The underlying mechanisms in the development and the variability in which individuals develop post-inflammatory hypopigmentation or hyperpigmentation are not well understood. Ruiz-Maldonado & Orozco-Covarrubias (16) proposed an inherited individual chromatic tendency which is based on "weak" or "strong" melanocytes and their tendency to respond to trauma or inflammation with either hypopigmentation or hyperpigmentation. Interestingly, a Singaporean study demonstrated that PIH tended to be more prevalent among Asians with darker skin, such as Malays and Indians, than those with lighter skin like Chinese, indicating that the degree of pigmentation may contribute more to the risk of PIH than race or ethnicity (17). The intensity of PIH may relate to higher skin phototypes, however studies are needed to establish this finding.

First-line therapy for PIH typically comprises application of topical depigmenting agents targeting different steps in melanin production and a vigilant sun protection (2). Topical tyrosinase inhibitors, such as hydroquinone, azelaic acid, kojic acid, arbutin, and certain licorice (glycyrrhiza) extracts, and other depigmenting agents, including retinoids, mequinol, ascorbic acid, niacinamide, N-acetyl glucosamine, and soy accelerate lightening of hypermelanosis. Topical therapy is typically effective for epidermal PIH; however, certain procedures, such as chemical peeling, laser and light therapy, may be useful in recalcitrant hyperpigmentation. The physician should be aware that the treatment of PIH itself may worsen the existing hyperpigmented condition. In essence, cosmetic camouflage to neutralise the PIH intensity is another beneficial therapeutic option. Patient education regarding ultraviolet light protection is an integral part that should not be overlooked or underestimated. Sun avoidance and protection not less than 2 weeks before fractional resurfacing is crucial in preventing PIH (4, 18).

Theoretically, corticosteroids induce anti-inflammatory proteins inhibiting phospholipase A2 and block the release of arachidonic acid and platelet activating factors from the cell membrane, therefore, preventing formation of potent inflammatory mediators, including prostaglandins and leukotrienes (10). Takiwaki and colleagues (12) formerly demonstrated that topical clobetasol propionate had the strongest suppression of UVB-induced erythema and pigmentation, followed by hydrocortisone butyrate and indomethacin. On the other hand, corticosteroid with its anti-proliferative effects mediated by inhibition of DNA synthesis and mitosis may interfere with fibroblast activity impairing the process of new collagen formation. However, we found no significant difference in scar improvement at 12-week follow-up. A longer follow-up period is necessary to warrant this observation.

Acneiform eruption may either be a side effect of AFR or an adverse effect of topical corticosteroids and/or petrolatum jelly. The incidence of acneiform eruptions (7.5% of the patients) noted in the current study was actually lower than that reported in our previous study (31% of the subjects) using a similar type of laser (4). This implies that short-term (2 days) use of topical corticosteroids postoperatively may not increase the risk of acneiform eruption. PIH may actually occur as a consequence of acneiform eruption, especially when it is not properly treated. Of note, our past experience of using topical corticosteroid postoperatively found that the risk of acneiform eruption was higher when we had the patients apply it for longer than 2 days. Thus, we currently recommend the patients to apply it only for the first 2 days postoperatively.

In clinical practice, choice of lasers and treatment parameters for atrophic acne scar should be carefully chosen according to the patient's skin phototype, the severity and/or types of the scars. However, even with special precautions PIH is still a common side-effect, especially in patients with dark skin. Therefore, the risk of PIH should be heightened in verbal and written informed consent given to the patient preoperatively.

A limitation of the current study is a small sample size. Nevertheless, statistically significant differences in the risk of PIH between 2 different postoperative treatment regimens were detected. Further study is needed to compare different potencies of topical corticosteroids and to find the optimal duration for its application, in order to get the maximum benefit in preventing PIH and minimising risks of its adverse effects.

Importantly, extra precaution should be taken when using high-potency topical corticosteroids in the immediate postoperative period of ablative laser procedures. An impairment of skin barrier function following skin ablation, and/or an immunosuppressive environment induced by corticosteroids may predispose the patients to infection. Postoperative infection in 2 patients was seen following the use of high-potency topical corticosteroids after receiving more than 80% facial skin resurfacing coverage (19). In fact, fractional laser resurfacing is a technique where only a fraction of the skin is thermally coagulated (5% of the skin was resurfaced in the current study), so the risk of skin barrier impairment was much less than that of the aforementioned study in which 80–100% skin coverage was resurfaced. In addition, animal studies have not found an increase in the infection rates in steroid-treated burn wounds (20).

In summary, short-term application of topical clobetasol postoperatively is associated with a decreased risk of PIH after ablative fractional resurfacing. This treatment regimen may be considered as a guideline for prevention of laser-induced PIH in dark-skinned patients.

ACKNOWLEDGMENT

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