**STUDY**

**Effect of Cold Air Cooling on the Incidence of Postinflammatory Hyperpigmentation After Q-Switched Nd:YAG Laser Treatment of Acquired Bilateral Nevus of Ota–like Macules**

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**Objective:** To investigate the effect of cold air cooling on the incidence of postinflammatory hyperpigmentation (PIH) after laser treatment in Asian patients.

**Design:** Randomized, controlled, split-face study.

**Setting:** Skin laser center of a university hospital.

**Patients:** Twenty-three Thai women with acquired bilateral nevus of Ota–like macules.

**Interventions:** Patients were treated using a 1064-nm Q-switched Nd:YAG laser at an average fluence of 7.0 J/cm² using a 3-mm spot size. The same laser fluence was used on both sides of the face in individual patients. One randomly selected face side of each patient was cooled using a cold air cooling device during and 30 seconds before and after laser irradiation, and the other side was irradiated without cooling.

**Main Outcome Measures:** Occurrence of PIH was objectively evaluated by measuring the melanin index using a spectrometer, and it was subjectively assessed by 2 non-treating physicians before treatment and once weekly for 4 weeks.

**Results:** Of the 21 patients who completed the study, 13 (62%) and 5 (24%) developed PIH on the cooled and uncooled sides, respectively. One patient (5%) had PIH on both the cooled and uncooled sides, and 2 (10%) did not experience PIH. The cooled sides were significantly more likely to become hyperpigmented after laser irradiation than the uncooled sides (relative risk, 2.6; 95% confidence interval, 1.13-6.00; \( P = .03 \)). The clinical evaluation corresponded to the spectrometer reading.

**Conclusion:** Epidermal cooling with cold air is associated with an increased risk of PIH after Q-switched Nd:YAG laser treatment.

**Trial Registration:** clinicaltrials.gov Identifier: NCT00287001

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POSTINFLAMMATORY HYPERPIGMENTATION (PIH) is a frequently encountered problem and represents the sequelae of various cutaneous disorders and therapeutic interventions. The pathogenesis of PIH includes an increase in melanin production and an abnormal distribution of this pigment. After trauma or cutaneous inflammation, melanocytes can react with increased or decreased production of melanin, reflected clinically as hyperpigmentation or hypopigmentation. Postinflammatory hyperpigmentation is probably the most common adverse effect of laser treatments in dark-skinned 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 minimized.

Acquired bilateral nevus of Ota–like macules (ABNOMs), or Hori nevus, is clinically characterized by blue-brown macules occurring bilaterally on the forehead, temples, eyelids, malar areas, nasal alae, and nasal root. Unlike the nevus of Ota, these pigmented lesions usually appear in the fourth or fifth decade of life in women (only rarely in men) and are not observed in the conjunctiva or mucous membranes of the mouth or nose. Histologically, active melanin-synthesizing dermal melanocytes are dispersed in the papillary and middle portions of the dermis. Q-switched lasers have been used successfully as a treatment modality. However, the incidence of transient PIH after laser treatment is as much as 50% to 73%.

Skin cooling has been used to protect the epidermis in a variety of laser dermatologic procedures, including leg vein treatment, hair removal, and port-wine stain removal. The use of epidermal cooling during laser treatment decreases procedure-associated pain, allows safer treatment of...
darker-skinned individuals, and allows the use of higher fluences. Studies to determine the benefit of epidermal cooling on the prevention of PIH after laser treatment are limited. Epidermal cooling is thought to reduce the non-specific thermal injury caused by the laser pulses and consequently to minimize the incidence of PIH.

The present study was performed to address the advantage of epidermal cooling on reducing the occurrence of PIH after laser treatment of ABNOMs. However, we found that epidermal cooling with cold air was associated with an increased risk of PIH after Q-switched Nd:YAG laser treatment. An unexpected finding was a clinically and statistically significant darkening of the cooled side compared with the uncooled side.

**METHODS**

Twenty-three Thai women with ABNOMs (Hori nevus) were enrolled in the study. The patients were randomized as to which side of the face would be treated with Q-switched Nd:YAG laser and a cold air cooling device vs Q-switched Nd:YAG laser alone by using a table of uniform random digits. The study protocol and informed consent documents were submitted and approved by the Ethics Committee on Research Involving Human Subjects, Faculty of Medicine Siriraj Hospital, Mahidol University. Written informed consent was obtained from each patient before enrollment.

**PATIENT CHARACTERISTICS**

The mean age of the patients was 43 years (range, 27-72 years). Their skin types were III (17/23) and IV (6/23). Patients who were pregnant or lactating, who were taking birth control pills or undergoing hormone therapy, or who participated in major outdoor activities were excluded. Patients who used bleaching agents, such as hydroquinone preparation, and those who received chemical peels, laser treatment, or intense pulsed light treatment before enrollment were also excluded.

**TREATMENT**

Lidocaine, 2.5%, and prilocaine, 2.5% cream (a eutectic mixture of local anesthetic) (AstraZeneca LP, Wilmington, Delaware) was applied to the lesions 1 hour before treatment, and a dressing (Tegaderm; 3M, St Paul, Minnesota) was used to occlude the area. Each patient received 1 Q-switched Nd:YAG laser treatment. The uncooled side of the patient’s face was always treated first, followed by the side with cold air cooling. The clinical end point was defined as the point of immediate whitening without bleeding and tissue splatter. The same fluence setting was used on both sides.

**COOLING TECHNIQUE**

A commercially available cold air cooling device (CRIOfat AIR Mini; CRIOfat Medizintechnik GmbH, Birkenfeld, Germany) was used at a cooling level of 4 for all treatments. This instrument works with a compressor system similar to those in refrigerators and uses ambient air to generate a permanent stream of cold air with a flow of 500 to 1000 L/min and temperatures as low as −30°C, depending on the cooling delivery system and the desired cooling level (range, 1-9). The nozzle-to-cooled surface distance was 3 cm (as suggested by the manufacturer). Relative humidity was 60%, and room temperature was approximately 25°C. The nozzle was held with a rotating motion during the treatment. The cooled side was always cooled during and 30 seconds before and after laser irradiation. The skin surface temperature, measured using an infrared thermometer (Mini-Temp MT4; Raytek Corp, Santa Cruz, California) during the treatment, was 4°C to 5°C.

Postoperatively, antibacterial mupirocin ointment (Bactroban Ointment; SmithKline Beecham Pharmaceuticals, Philadelphia, Pennsylvania) was applied to the treated area. Patients were instructed to cleanse the treated sites gently with tap water and to reapply the mupirocin ointment 4 times a day until all crusting had subsided. After crusting completely healed, all the patients were instructed to wear a broad spectrum sunscreen with a sun protection factor of 40 and were also asked to avoid sun exposure, which could cause hyperpigmentation.

**CLINICAL EVALUATION**

Masked assessment of the occurrence of PIH in all the patients was made by 2 expert dermatologists from the digital photographs taken before treatment (baseline) and 1, 2, 3, 4, and 12 weeks after laser treatment. Photographs were taken using a digital camera (D70s; Nikon Corporation, Tokyo, Japan) equipped with a 60-mm lens (Nikkor; Nikon Corporation) and Canfield TwinFlash (Canfield Scientific Inc, Fairfield, New Jersey). All the photographs were taken in raw format with identical conditions.
and camera settings. Standardized views (face front and 45° oblique) were used. The liquid crystal display monitor was calibrated for precise on-screen displays using a colorimeter (Spyder2; Colorvision Inc, Lawrenceville, New Jersey). Clinical observations for cutaneous changes (specifically, erythema, urticaria, blistering, dyspigmentation, and scarring) were conducted at 1-hour and 1-week intervals after cold air exposure.

Observable skin changes were graded on the following scale: 0, absent; 1, minimal (light pink; barely perceptible skin elevation; whitening of skin; no evident blister); 2, mild (light red/pink; slight skin elevation; skin wrinkling; no well-formed blister); 3, moderate (red; clearly visible urticaria; flaccid blisters); and 4, severe (very red; pronounced urticaria; tense blisters). Clinical evaluation for the improvement in lesional pigmentation was subjectively graded at baseline and week 12 using a quartile grading scale as follows: poor, less than 25%; fair, 25% to 50%; good, 51% to 75%; and excellent, more than 75% improvement.

COLOR READING

The designated lesions of pigmented macules on both sides of the face were marked on every patient and mapped with a translucent sheet at the first visit to ensure consistency of location. The degree of lesion lightening was defined as the percentage of darkness reduction compared with baseline. The degree of pigmentation was assessed using a handheld reflectance spectrometer (DermaSpectrometer; Cortex Technology, Hadsund, Denmark). By emitting red light at 655 nm and measuring the absorption coefficients in the skin, the instrument provides a readout of a melanin index (M-index) based on the absorption characteristics of the skin pigmentation. During measurements, the device was placed perpendicularly on the skin; blanching was minimized by applying light pressure. The value used was the average of 3 measurements at each site at each assessment. A higher M-index value indicates increased saturation toward darkness.

STATISTICAL ANALYSIS

Two-tailed paired t test analyses using statistical software (SPSS version 14; SPSS Inc, Chicago, Illinois) were performed to compare mean M-index values for each treatment technique and at baseline vs the 12-week follow-up visit. Relative risk was calculated using statistical software (Epi Info version 3.3.2; Centers for Disease Control and Prevention, Atlanta, Georgia). P < .05 was considered statistically significant.

Of the 23 patients, 21 completed all the follow-up visits. Two patients were withdrawn from the study because they did not attend scheduled visits. Acute erythema was noted in 18 of 21 patients (86%), 1+ erythema was observed in 16 of 21 patients (76%), and 2+ erythema was present in 2 of 21 patients (10%). One hour after treatment, the redness disappeared in 12 of 18 patients (67%) who developed erythema. In all the patients, the erythema resolved in 24 hours. One patient each with skin types III and IV developed 1+ urticaria. All urticaria resolved by the day 1 follow-up visit. No blistering was observed in any patients.

The crusting healed completely within 1 and 2 weeks of treatment in 17 of 21 patients (81%) and 4 of 21 patients (19%), respectively. No difference in crusting resolution rates was observed between the cooled and uncooled sides. No patients developed hypopigmentation or scarring. All the patients noted significant pain reduction on the cooled side during laser treatment. No postoperative analgesic treatment was required beyond the application of mupirocin ointment and ice compresses.

As judged by the 2 expert dermatologists, of the 21 patients who completed the study, 13 (62%) developed PIH on the cooled side, and 5 (24%) had PIH on the uncooled side (Figures 1, 2, 3, and 4). One patient (5%) had PIH on both the cooled and uncooled sides, and 2 (10%) did not experience PIH. The cooled sides were 3 times more likely than the uncooled sides to develop PIH after laser treatment (relative risk, 2.6; 95% confidence interval, 1.13-6.00; P = .03). The onset of PIH was at week 1, 2, 3, and 4 in 5% (1/21), 62% (13/21), 14% (3/21), and 10% (2/21) of the patients, respectively. The PIH was completely resolved 12 weeks after laser treatment in all the patients except 1 with skin type IV, who developed PIH on the cooled side.

All the patients showed less than 25% overall lightening of the pigmented macules at week 12. No difference in clinical improvement was observed regarding the cooling used on 1 side during treatment. At baseline, there was no significant difference in the M-index values of the

Figure 2. The left (cooled) (A) and right (uncooled) (B) sides of the face 1 week after treatment.
cooled and uncooled sides \( (P = .17) \). At week 12, there was also no significant difference in the M-index values of the lesions on the cooled \( (P = .07) \) and uncooled \( (P = .55) \) sides compared with baseline. The M-index value of all areas considered to have PIH was significantly increased compared with the baseline value \( (P = .03) \).

**COMMENT**

Postinflammatory hyperpigmentation is one of the most common adverse effects in dark-skinned patients after laser treatment. It is not life threatening, but PIH may cause substantial psychological problems. The incidence of transient PIH after carbon dioxide laser resurfacing is approximately 37% in patients with all skin types\(^{15}\) and nearly 70% in those with skin type IV or higher.\(^{16}\)

Hori nevus or ABNOMs is a common pigmented disorder in Asian individuals. Q-switched lasers provide favorable treatment responses, but transient PIH after laser irradiation affects as much as 50% to 73% of patients and can last for many months.\(^{11,17}\) Postinflammatory hyperpigmentation takes a long time to dissipate. The treatment of PIH is difficult and time-consuming, often lasting many months to achieve the desired results, which causes frustration in patients and physicians.\(^{1,2}\) Thus, various attempts to reduce the occurrence of PIH after skin laser surgery have included sun avoidance, use of preoperative and postoperative treatment regimens, and techniques for epidermal protection.

Current commercial cooling methods and devices include passive cooling with aqueous gel, active cooling with water or refrigerated air, and dynamic active cooling with cryogen spray. Lowering the temperature of the skin’s surface is a method of selectively controlling the depth at which heat is produced in the skin by lasers or pulsed light sources. Cooling of the epidermis can prevent its temperature elevation from exceeding the threshold for thermal injury.\(^{12}\) Minimizing the nonspecific thermal injury to the skin surface caused by the laser pulses may therefore lower the incidence of PIH.

A previous study\(^{18}\) of a freeze injury in normal human skin showed that a brief (5-second) freezing of liquid nitrogen caused hypopigmentation, with a periph-

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**Figure 3.** The left (cooled) (A) and right (uncooled) (B) sides of the face 2 weeks after treatment. Note the postinflammatory hyperpigmentation of the lesions on the left (cooled) side of the face.

**Figure 4.** The left (cooled) (A) and right (uncooled) (B) sides of the face 12 weeks after treatment. Note the disappearance of the postinflammatory hyperpigmentation on the left (cooled) side of the face.
eral rim of hyperpigmentation in all frozen lesions. Similarly, a recent study by Datrice et al. also found that transient hyperpigmentation occurred after cryogen spray cooling exposure in individuals with skin type III or higher, and all hyperpigmentation was resolved by 8 weeks without medical intervention.

In trying to address the possible causes of this occurrence, we tested the effect of the cold air cooling in 2 patients with untreated ABNOMs (not in the present study). The same cooling techniques were performed without laser irradiation on 1 side of the face of each patient. The patients were followed up every week for 4 weeks. However, none of the patients developed PIH on the cold air-exposed side. Thus, it is unlikely that cold air exposure alone is the mechanism causing PIH. However, some inflammatory triggers from the laser irradiation may underlie the increased incidence of PIH in the present study.

The underlying mechanisms and the variability individuals show for developing hyperpigmentation or hypopigmentation are not well understood. An inherited individual chromatic tendency based on “strong” or “weak” pigmentation are not well understood. An inherited individual chromatic tendency based on “strong” or “weak” pigmentation are not well understood. An inherited individual chromatic tendency based on “strong” or “weak” pigmentation are not well understood. An inherited individual chromatic tendency based on “strong” or “weak” pigmentation are not well understood. An inherited individual chromatic tendency based on “strong” or “weak” pigmentation are not well understood. An inherited individual chromatic tendency based on “strong” or “weak” pigmentation are not well understood.

In conclusion, the mechanism by which cold air cooling is associated with an increased risk of PIH after laser treatment is unknown. It is possible that the mechanism was a melanocyte’s or keratinocyte’s responses to the laser pulses together with cold air exposure. Future studies should address the question of whether the other methods of epidermal cooling are associated with an increase risk of PIH. Of particular interest is the mechanism that underlies the cause of hyperpigmentation after cold air cooling.

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References: