

Clinicopathologic Efficacy of Copper Bromide Plus/Yellow Laser (578 nm with 511 nm) for Treatment of Melasma in Asian Patients

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BACKGROUND Melasma is a common pigmentary disorder in Asians. Although the pathogenesis of melasma is not yet fully understood, there are several hypotheses supporting angiogenetic factors related to some types of melasma.

OBJECTIVE To test the efficacy of copper bromide laser in the treatment of Korean women with melasma.

MATERIALS AND METHODS Clinical parameters included physician and patient assessment and Melasma Area and Severity Index score. The intensity of pigmentation and erythema was measured using a chromometer. To evaluate histopathologic changes, punch biopsies from melasma were obtained from four patients. Immunohistochemical staining for Melan-A, endothelin 1, CD34, and vascular endothelial growth factor (VEGF) antigen of the melasma lesions was observed.

RESULTS Mean MASI score decreased dramatically after treatment. Patients exhibited telangiectatic erythema within the melasma lesion. The values of L* reflecting intensity of pigmentation increased, and the values of a* as the measurement of redness decreased after the treatments. Expression of Melan-A, CD34, endothelin-1, and VEGF decreased after treatment.

CONCLUSION The potential application of an antiangiogenetic laser for the treatment of melasma specially accompanied by pronounced telangiectasia in Asian skin is a possible treatment option.

The authors have indicated no significant interest with commercial supporters.

Melasma is a common acquired symmetrical hypermelanosis of sun-exposed areas of the skin that is common in Asian women. The major etiological factors are genetic influences, exposure to ultraviolet (UV) radiation, and sex hormones,¹ although the pathogenesis of melasma is not fully understood.

Recent studies have suggested a possible connection between vessels and cutaneous pigmentation. Human melanocytes may respond to angiogenic factors because normal human melanocytes express functional vascular endothelial growth factor (VEGF) receptors.² Also, it has been reported that the topical plasmin inhibitor tranexamic acid is effective in the treatment of UV light-induced hyperpigmentation.³ Localized microinjection of

tranexamic acid has improved melasma in vivo.⁴ These in vitro and in vivo findings suggest that interactions between the altered cutaneous vasculature and melanocytes may have an influence on the development of hyperpigmentation in the overlying epidermis. In some types of melasma, pronounced telangiectatic erythema confined to melasma-lesional skin has been observed. Increased vascularity is one of the major histologic findings in melasma.⁵ Interactions between the altered cutaneous vasculature and melanocytes may influence the development of melasma.

Traditional therapies, including depigmenting agents (e.g., hydroquinone, azelaic acid), chemical peels (e.g., glycolic acid, b-hydroxyl acid, trichloroacetic acid), topical steroids, and sunscreens have some

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therapeutic effect but are often unsuccessful in the treatment of refractory melasma. The use of lasers in the treatment of melasma is controversial. Facial resurfacing with an erbium laser or a pulsed carbon dioxide laser, alone or in conjunction with a Q-switched alexandrite laser, have reportedly been successful, but they result in significant downtime, and there is a risk of adverse sequelae.^{6,7} Fractional laser therapy with a 1,550-nm erbium fiber laser has recently been investigated in a pilot study.⁸

Copper bromide lasers emit a green beam at a wavelength of 511 nm, which can be used to treat pigmentary lesions, and a yellow beam at a wavelength of 578 nm, which can be used to treat vascular lesions.^{9,10} This study is a report of the clinical efficacy and immunohistochemical changes after the use of copper bromide Plus/Yellow Laser (Norseld Pty Ltd, Adelaide, Australia) (578 nm with 511 nm) to treat melasma in Asian patients.

Materials and Methods

Patients

Ten Korean women aged 32 to 51 (mean 40.7) with melasma were enrolled in this clinical study between December 2007 and April 2008. Patients aged 30 to 60 with clinically diagnosed melasma were eligible to participate in this study. The melasma was diagnosed through physical examinations and confirmed using histological examinations.

Pregnant or nursing woman; patients with excessive photosensitivity to normal sunlight, inflammatory disease of the skin, open wounds in the area of treatment, and active herpes simplex; patients exhibiting symptoms of severe stress; patients refusing to give informed consent; patients with facial congenital nevi; patients using oral or topical medications that can affect the response to visible light; patients using oral contraceptive pills; patients who had ever used topical steroids, including triple combination cream; patients treated with topical hypopigmenting agents, such as hydroquinone,

tretinoin, kojic acid, and azelaic acid, and other lasers or intense pulsed light less than 3 months before were excluded.

The duration of melasma ranged from 6 months to 30 years (mean 9.4 years). Seven patients had Fitzpatrick skin type III and three skin type IV. According to Wood's Lamp Assessment, 60% of patients (6/10) had a mixed-type melasma, and 40% (4/10) had an epidermal-type melasma. In the distribution of melasma, seven patients had a malar pattern, and three had a centrofacial pattern. The centrofacial pattern was observed in three patients: the melasma involved the cheeks, forehead, upper lip, and chin. The malar pattern, located in the malar region, was observed in seven patients. All subjects were instructed to avoid the use of bleaching agents during the course of the treatment and for 3 months of follow-up. They were also instructed on proper sun protection and the use of broad-spectrum sunscreens.

Informed written consent was obtained from each patient before skin sampling. The ethical committee of Chung-Ang University Yong-San Hospital approved the study. There were no conflicts of interest.

Treatment Protocols

Plus/Yellow Laser was used for all treatments. This copper bromide laser produces two wavelengths that can be emitted separately or together: green (511 nm) and yellow (578 nm). The green and yellow lasers are simultaneously produced in a 1:9 ratio in plus mode. The yellow wavelength is adjustable up to a maximum of 2.1 W. The copper bromide laser emits quasicontinuous pulse trains with a pulse width of 24 ns and a pulse repetition rate of 12 kHz. Treatment fluences ranged from 12 to 14 J/cm². A spot size 1.0 mm was used. The emission time was 50 to 60 ms, and the off time was 70 ms, with 7.7 to 8.3 pulses per second and four passes.

Each patient received four treatments at 2-week intervals administered to the face. A chilled, colorless ultrasonic gel was applied directly to the skin. No

topical or local anesthetic was used in any of the patients, and the eyes were always protected. The patients were instructed to avoid the use of any bleaching or antiwrinkle agents during the course of the treatment. They were also instructed to avoid sun exposure and wear broad-spectrum sunscreen during and after the treatment.

Evaluation Criteria

Evaluation of skin lesions was performed before each treatment session and 1 month after the final treatment. All patients were followed up at 3 and 6 months after the final treatment. Five standard digital photographs were taken (EOS 40D, 6.0 megapixels, Canon, Tokyo, Japan) before each treatment session.

The clinical assessment consisted of the physicians' overall assessment and patient self-assessment of the extent of melasma. Clearance was estimated as a percentage from 0 (no change) to 100 (complete disappearance of the telangiectasia and pigmented lesions).

Two investigators independently evaluated Melasma Area and Severity Index (MASI) scores (Table 1) before each session and 1 month after the last session.

For a more objective assessment, the lesional melasma of 10 patients was evaluated using a skin color measuring device at the highest point on the cheekbones before each session and 1 month after the last session. The intensity of pigmentation and erythema were measured using skin reflectance with a tristimulus color analyzer (Chromameter CR-400, Minolta Co., Tokyo, Japan) and expressed in the $L^*a^*b^*$ system. This system allows colors to be quantified according to three axes: white-black or lightness (L^*), red-green or chrome (a^*), and yellow-blue or hue (b^*). The L^* parameter reflects the intensity of pigmentation, and the a^* parameter measures redness.

To evaluate histopathologic changes, 2 mm punch biopsies from lesional melasma were obtained from four patients under local anesthesia before and 3 months after the last treatment. The tissue samples were prepared for light microscopic study using 10% formalin fixation. Three- μ m-thick paraffin-embedded tissue sections were processed for routine immunohistochemistry. A hematoxylin and eosin (H&E) stain was used to study the general histopathological changes in the melasma skin. Melanin pigment was visualized using Fontana-Masson staining performed using the usual methods without an eosin background stain. The immunohistochemical staining was performed on 4- to 5- μ m-thick

TABLE 1. Melasma Area and Severity Index (MASI) Scoring System

A: Percentage of the total area involved

0 = none

1 = < 10

2 = 10–29

3 = 30–49

4 = 50–69

5 = 70–89

6 = 90–100

D: Darkness of the melasma compared to normal skin

H: Homogeneity of the hyperpigmentation

0 = normal skin color without evidence of involvement

1 = barely visible hyperpigmentation/specks of involvement

2 = mild hyperpigmentation/small patchy areas of involvement < 1.5 cm diameter

3 = moderate hyperpigmentation/patches of involvement > 2 cm diameter

4 = severe hyperpigmentation/uniform skin involvement without any clear area

MASI score = Forehead $0.3(D + H)A$ + Rt. Malar $0.3(D + H)A$ + Lt. Malar $0.3(D + H)A$ + Chin $0.1(D + H)A$.

serial paraffin-embedded sections mounted on poly-L-lysine-coated slides. The sections were deparaffinized, and the endogenous peroxidase activity was blocked with 3% hydrogen peroxide for 15 minutes. Then the sections were subjected to antigen retrieval using pressure cooking in 0.01M citric acid (pH 6.0, 125°C) for 3 minutes. These sections were then incubated with monoclonal anti-CD34 antibody (1:200 dilution, Cat. No. MS-363, NeoMarker, Fremont, CA), monoclonal anti-Melan-A antibody (1:50 dilution, Cat. No. M7196, Dako, Carpinteria, CA), monoclonal anti-Endothelin 1 antibody (1:500 dilution, Cat. No. MA3-005, Affinity Bioreagents, Golden, CO), and polyclonal anti-VEGF antibody (1:100 dilution, Cat. No. Sc-152, Santa Cruz Biotechnology, Inc., Santa Cruz, CA); incubated for 24 hours at room temperature; and developed using EnVision Plus reagent (Dako). Amino ethyl carbazole was used as the substrate. The slides were counterstained with Mayer's hematoxylin.

Results

All of the patients completed the full course of the study. The representative case with a marked response is shown in Figure 1. The results of the physicians' overall assessments and the patients' subjective self-assessments have been summarized in Table 2.

The mean MASI score decreased dramatically, from 12.3 ± 3.2 before treatment to 9.5 ± 3.5 at the 1-month follow-up visit ($p < .05$). Table 3 summarizes the clinical findings and changes in mean MASI scores in the 10 patients.

Some degree of telangiectatic erythema was noticed within the pigmented patches in patients with melasma. The values of L^* were 57.3 ± 3.4 in the melasma lesions and 62.5 ± 1.3 in perilesional normal skin. The values of a^* were higher in the melasma lesions (mean 13.8 ± 1.8) than in perilesional normal skin (mean 11.3 ± 1.2).

In the melasma lesion at the highest point of the cheekbone, L^* increased from 56.7 before treatment to 57.0 after one session; increased to 57.6 after two sessions, 59.0 after three sessions, and 59.2 after four sessions; and dropped to 58.4 at the 1-month follow-up visit ($p < .01$, Figure 2A). The subjects exhibited telangiectatic erythema within the brownish patches on physical examination before treatment. The a^* values decreased according to the treatments. Quantification of a^* at the highest point of the cheekbones revealed a substantial decrease from 14.8 before treatment to 13.5 after one session, 13.3 after two sessions, 12.0 after three sessions, and 10.9 after four sessions and a slight increase to 11.8 at the 1-month follow-up visit ($p < .01$, Figure 2B).

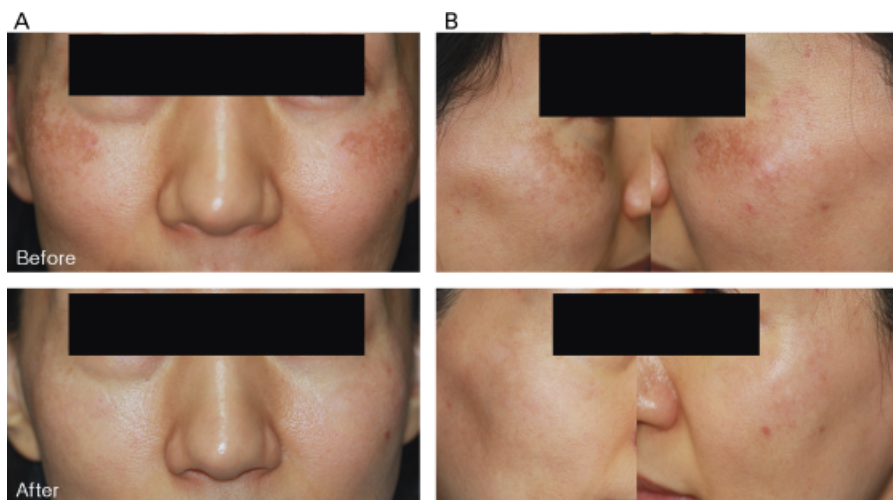


Figure 1. A 42-year-old woman (A) before and (B) 1 month after five copper bromide dual yellow laser treatments.

TABLE 2. Average Improvement (% Change)

	<i>Telangiectasia</i>	<i>Pigmented Lesions</i>
Patient	82.4 ± 12.6	71.5 ± 11.2
Clinician	76.5 ± 8.5	65.4 ± 8.2

The general histopathological features of pretreatment melasma were compared in the H&E-stained sections using post-treatment biopsy specimens. All melasma specimens before treatment showed varying degrees of epidermal hyperpigmentation, rete ridge flattening, and epidermal thinning; a slightly greater number of dermal melanophages; and perivascular lymphohistiocytic infiltration. Basal pigmentation was less after treatment. Fontana-Masson staining and immunohistochemistry for Melan-A were performed to investigate changes in melanin in

the melasma lesions after treatment. In the Fontana-Masson-stained sections, the amount of melanin in the basal layer of epidermis was lower after the treatment. Melan-A immunostaining showed a marked decrease of melanosomes detected by Melan-A in the epidermis (Figure 3A). To examine whether vascularity in the melasma lesions was lower after the treatment, the expression of CD34 and VEGF were examined using immunohistochemistry. CD34 immunostaining showed a marked decrease in the number and size of blood vessels in the dermis (Figure 3B). Less positive immunoreactivity against VEGF was noticed in keratinocytes after treatment (Figure 3C).

Clinically, the treatment was tolerated well without anesthetics. Transient erythema was observed on the laser-treated site until 2 days after the laser treatment, but none of the patients noted any long-term adverse effects, including scarring and postinflammatory hyperpigmentation and hypopigmentation. Long-term follow-up examination using photographs was done 3 months after the last treatment. At the 3-month follow-up visit, melasma lesions show no change from 1 month after the last treatment. At 6 months after the last treatment, recurrence of melasma was observed in three patients (patient numbers 6, 9, and 10).

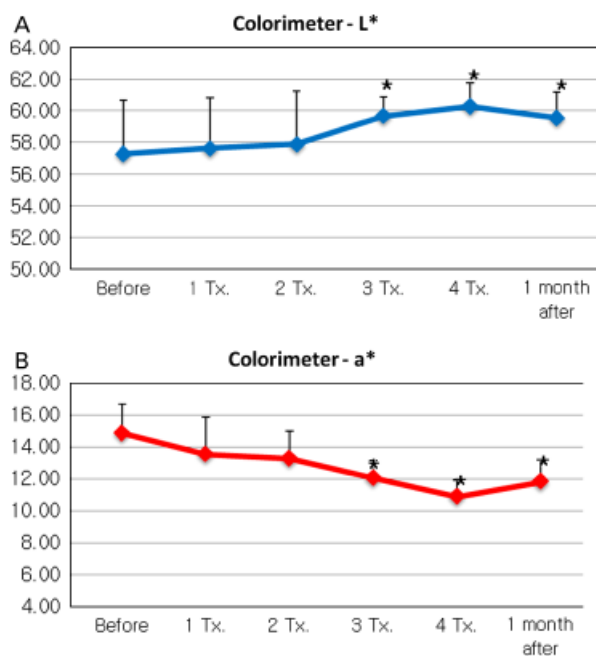


Figure 2. (A) At the highest point of the cheekbone, L^* increased from 56.7 before the treatment to 57.0 after one session, 57.6 after two sessions, 59.0 after three sessions, and 59.2 after four sessions and dropped to 58.4 at the 1-month follow-up visit ($p < .01$). (B) The a^* values decreased according to the treatments. Quantification of a^* at the highest point of the cheekbones revealed a substantial decrease from 14.8 before the treatment to 13.5 after one session, 13.3 after two sessions, 12.0 after three sessions, and 10.9 after four sessions and a slight increase to 11.8 at the 1-month follow-up visit ($p < .01$).

Discussion

The copper bromide laser is unique because it offers a dual-wavelength output; 511 nm in the green and 578 nm in the yellow are produced simultaneously. It emits light with a short pulse duration of 24 ns. The pulse repetition rate is in the range of 12,000 Hz. This repetition rate is high enough that the beam appears to be continuous to the human eye, that is, quasicontinuous. The individual pulse cannot supply sufficient thermal energy to coagulate the vessels being treated. The summation of the thermal energy from numerous pulses will coagulate the vessels. Favorable results have been reported when treating facial telangiectasia with the copper bromide laser.^{11,12} The advantage of treating pigmented

TABLE 3. Clinical Findings and Changes of Melasma Area and Severity Index (MASI) Score in 10 Patients with Melasma

Patient	Age	Type	Pattern	MASI Score	
				Pretreatment	Post-Treatment
1	38	Epidermal	Malar	10.8	6.5
2	32	Epidermal	Malar	12.6	9.8
3	33	Epidermal	Malar	8.4	5.2
4	42	Epidermal	Malar	14.4	12.2
5	36	Mixed	Malar	11.2	9.6
6	43	Mixed	Centrofacial	18.2	15.6
7	47	Mixed	Malar	7.8	5.4
8	40	Mixed	Malar	10.6	6.8
9	45	Mixed	Centrofacial	15.4	13.0
10	51	Mixed	Centrofacial	13.2	10.8
Mean	40.7 ± 6.1			12.3 ± 3.2	9.5 ± 3.5

lesions with green 511-nm light is that melanin absorbs this wavelength to a greater extent, producing more selective damage. The short-pulse, high repetition rate output produced by the copper bromide laser helps limit thermal destruction to the melanin-containing epidermis. It has been shown to effectively photocoagulate a variety of superficial vascular and pigmented lesions. In recent studies, yellow light has been tested for collagen synthesis and photorejuvenation.^{13,14} As complications, transient hyperpigmentation occurs in approximately 10% of patients treated with the copper bromide laser for facial telangiectasia. Hypopigmentation and hypopigmented scars can also occur but are infrequent.

Melasma is a common, acquired pigmentary disorder in Asians. A major clinical characteristic of melasma is hyperpigmented patches, but additional characteristics such as pronounced telangiectatic erythema confined to the melasma lesional skin have been observed in some types of melasma. Although the pathogenesis of melasma is not fully understood, a possible pathogenesis is that a wide variety of endogenous factors that the melanocyte itself produces (autocrine) alter the melanocytes or a local (paracrine) or systemic (endocrine) environment. These factors mediate signals to induce proliferation, differentiation, dendricity, morphology, migration, and pigmentation of melanocytes.¹⁵⁻¹⁷ It has

recently been suggested that interactions between the cutaneous vasculature and melanocytes might have an influence on the development of pigmentation and that the dermal environment may have an important role in the development of melasma.² There are several hypotheses supporting angiogenic factors that are related to some types of melasma.

CD34 is a heavy, glycosylated molecule that is expressed in the hematopoietic cells, hematopoietic progenitor stem cells, and endothelial cells in blood vessels, but it is not found in lymphatics or mast cells. The melanoma antigen recognized by T-cells (MART-1/Melan-A) is a melanocytic differentiation marker. The antigen that affects the expression, stability, trafficking, and procession of Pmel 17 within the melanosome is expressed in normal melanocytes, common nevi, and malignant melanoma. UV irradiation induced on the keratinocyte and secreted by vascular endothelial cells induces ET1. This antigen affects melanogenesis by activating tyrosinase and increasing TRP-1 levels, melanocyte proliferation, and dendrite formation. Keratinocytes associated with wound healing, psoriasis, UV irradiation, fibroblasts in tissue stroma, and tumor cells secrete VEGFs. VEGF is associated with cutaneous angiogenesis (vascular endothelial cells), and it affects melanogenesis by stimulating the release of arachidonic acid and activates

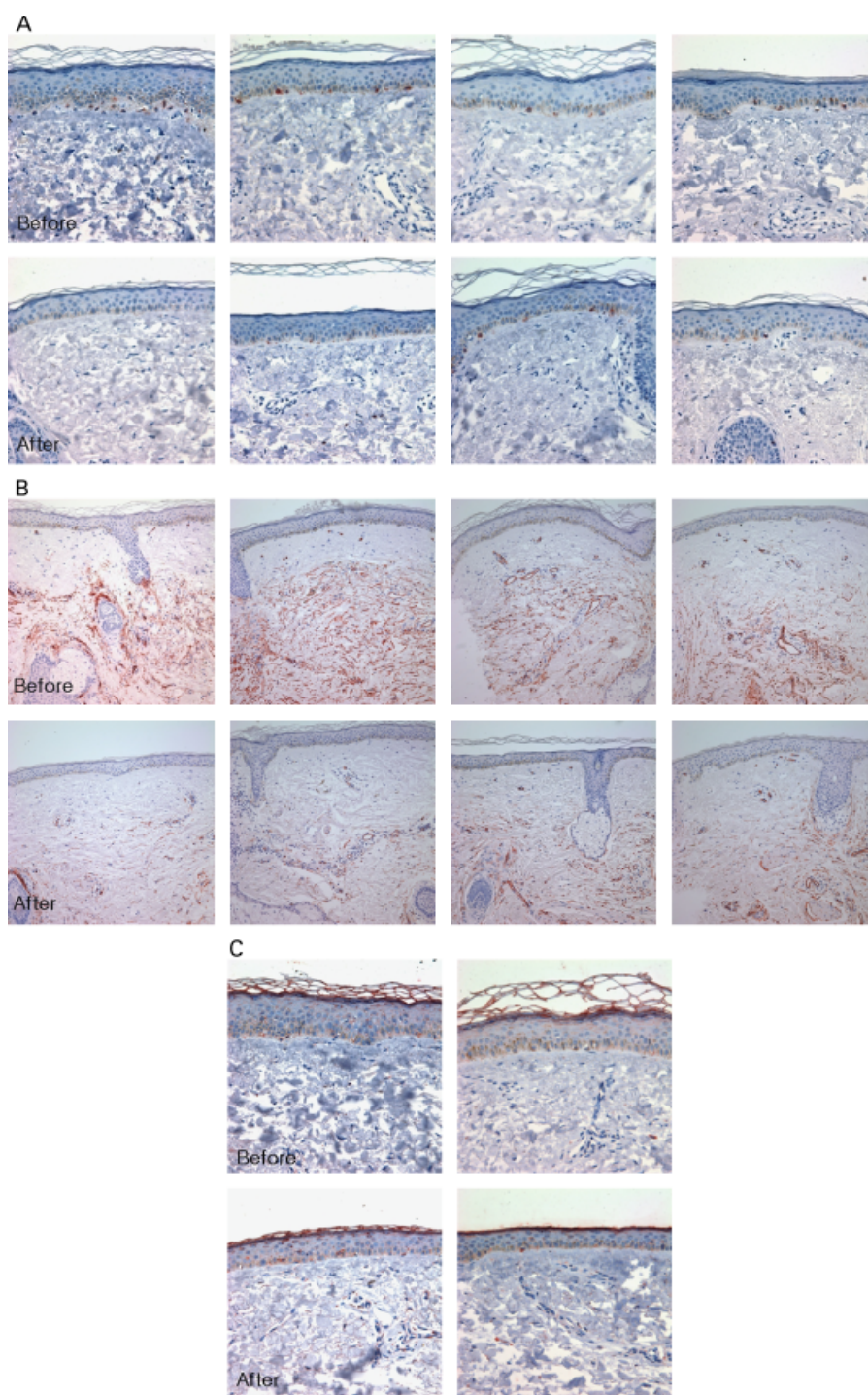


Figure 3. (A) Melan-A for melanocyte. Marked decrease of melanosome detected by Melan-A in the epidermis ($\times 400$). (B) CD34 for endothelial cells of blood vessels. Marked decrease in the number and size of blood vessels in the dermis ($\times 200$). (C) Vascular endothelial growth factor (VEGF) in keratinocytes. Slightly decreased expression of VEGF in the keratinocytes ($\times 400$).

phospholipase A2. A possible effect of VEGF on function of melanocytes is expected in that human melanocytes express VEGF receptors.

Epidermal keratinocytes have a primary role in the physiology and pathology of cutaneous angiogenesis.¹⁸ Moreover, epidermis-derived VEGF is regarded as a potent angiogenic factor in many cutaneous diseases.¹⁹ Keratinocytes in the skin constitutively produce VEGF. Its production is up-regulated in psoriasis, wound healing, and other states of increased skin angiogenesis, as well as by UV irradiation.^{20–22} In particular, several reports have suggested that VEGF is induced in human keratinocytes after UV exposure.^{23,24} Kim and colleagues²⁵ demonstrated that acute exposure to UV radiation triggers angiogenesis via VEGF induction and MEK–ERK1/2 activation and that all-trans retinoic acid (tRA) inhibits UV-induced ERK1/2 activation, VEGF upregulation in keratinocytes, and angiogenesis in human skin. Also, it was recently reported that the topical plasmin inhibitor is an effective treatment for UV-induced hyperpigmentation.³ Lee and colleagues⁴ suggested that the intralesional localized microinjection of tranexamic acid can be used as a potentially new therapeutic modality for the treatment of melasma. The following inflammatory mediators have been reported to increase melanogenesis: interleukins (IL-1a, IL-1b, and IL-6), tumor necrosis factor alpha, eicosanoids (prostaglandins D2, E2, F2, and leukotriene B4), and histamine. Tranexamic acid inhibits UV-induced plasmin activity in keratinocytes by preventing the binding of plasminogen to the keratinocytes, which ultimately results in fewer free arachidonic acids and a diminished ability to produce prostaglandins, and this decreases melanocyte tyrosinase activity.

Our results show that expression of VEGF in keratinocytes decreased slightly after treatment with 578-nm copper bromide yellow laser. Therefore, we expected that the yellow laser would have some direct or indirect effects on melanogenesis through the effect on VEGF in keratinocytes, dermal angiogenesis, and inflammatory mediators, but in vitro

and in vivo studies are needed for demonstrating a clear mechanism for the antiangiogenic and anti-melanogenic effects of yellow laser.

Kim and colleagues²⁵ demonstrated that greater vascularity is one of the major findings in melasma and that VEGF may be a major angiogenic factor for altered vessels in melasma. The biological role of cutaneous blood vessels in the pathogenesis of melasma remains unclear. VEGF is known to stimulate the release of arachidonic acid and the phosphorylation and activation of cytosolic phospholipase A2.²⁶ It is possible that the resulting metabolites from the arachidonic acid pathway affect melanogenesis.²⁷ Human melanocytes may respond to angiogenic factors because normal human melanocytes express functional VEGF receptors.² Therefore, VEGF may have a direct influence on melanocyte behavior through its receptor.

The copper bromide Plus/Yellow Laser, which produces green (511 nm) and yellow (578 nm) wavelengths, affects the altered dermal vasculature and epidermal melanin pigmentation in melasma lesions. It is unclear why melasma is improved after yellow laser treatment. It is also not clear whether this laser has a direct effect on the dermal vasculature and epidermal melanin or an indirect effect on the epidermal VEGF. In vitro and in vivo studies are needed to demonstrate a clear mechanism for the antiangiogenic effects of yellow laser. We suggest that this antiangiogenic laser may be a treatment option for melasma specially accompanied by pronounced telangiectasia. A study using more vascular-specific lasers such as V-Beam (Candela Corporation, Wayland, MA) for the treatment of melasma may provide us with new insights into the pathogenesis of melasma. Further controlled split-face designed studies are needed to achieve more improvements for melasma treated with copper bromide Plus/Yellow Laser.

Acknowledgment This study was supported by the Chung-Ang University Research Grants in 2010.

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