ORIGINAL ARTICLE

Dose Response of Combination Photorejuvenation Using Intense Pulsed Light–Activated Photodynamic Therapy and Radiofrequency Energy

Jeffrey A. Hall, MD; Pamela J. Keller, RN; Gregory S. Keller, MD

Objective: To report the results of a dose-response study using a novel photorejuvenation regimen consisting of intense pulsed light–activated photodynamic therapy and radiofrequency energy in patients with Fitzpatrick skin types I through III.

Methods: A combination intense pulsed light and radiofrequency device (Syneron Medical Ltd, Yokneam, Israel) was used in combination with the topical photosensitizer aminolevulinic acid (ALA) (Levulan Kerastick; DUSA Pharmaceuticals Inc, Wilmington, Mass). Duplicate titration trials were performed on the dorsal forearm skin of 3 patients with Fitzpatrick skin types I through III. Multiple treatments, with varying times of application of ALA (30 minutes and 1, 2, and 3 hours) and intense pulsed light fluence (24-30 J/cm^2), were completed to determine a minimal erythema dose and a maximal tolerated dose based on epidermal reaction (erythema and crusting) and patient discomfort. Radiofrequency energy levels were constant in all treatment groups.

Results: The ALA application time of 1 to 2 hours for all skin types and fluence levels of 26 to 28 and 24 to 26 J/cm^2 for Fitzpatrick skin types I/II and III, respectively, were determined to be the minimal erythema dose. The ALA application times of 2 to 3 hours and fluence levels of 28 to 30 and 26 to 28 J/cm^2 for skin types I/II and III, respectively, were determined to be the maximal tolerated dose and resulted in severe erythema and crusting. The presence of severe erythema and discomfort precluded longer ALA exposure and higher fluence levels. No epithelial breakdown was observed at any treatment levels.

Conclusion: The dose-response results defining the minimal erythema dose and the maximal tolerated dose of intense pulsed light–activated photodynamic therapy and radiofrequency energy have led to the development of 2 photorejuvenation protocols based on skin type and severity of photodamage.

Arch Facial Plast Surg. 2004;6:374-378

PHOTODAMAGE CAUSED BY long-term UV light exposure results in the characteristic epidermal and dermal changes of solar elastosis, which have been well defined histologically. Epidermal changes include thinning and increased pigmentation in the basal layer. The more critical dermal actinic changes include disorganization and loss of collagen bundles and clumping of elastic fibers.[1] These changes cause destruction of the elastic components of the dermis. The visible signs of photodamage include wrinkling, coarse skin texture, pigmentation changes, telangiectases, and, in some cases, premalignant actinic keratoses (AKs) or cutaneous malignant neoplasms. The most effective means of improving visible actinic changes have traditionally involved epithelial ablation (eg, chemical peels, dermabrasion, and laser resurfacing). To avoid the prolonged recovery period and possible scarring that have been associated with these ablative techniques, multiple nonablative techniques have been developed.[1] Intense pulsed light (IPL) is a broadband light source that emits a continuous spectrum in the 515- to 1200-nm range and is a well-established nonablative therapy for most components of solar damage, excluding AKs.[1-3]

Photodynamic therapy (PDT) refers to the therapeutic use of a photochemical reaction catalyzed by the application of light in the presence of a photosensitizing compound to achieve a local therapeutic effect. The reaction causes a localized tissue destruction thought to be mediated by generation of a high-energy singlet oxygen. Photodynamic therapy has been used to treat a multitude of diseases, including aerodigestive tract tumors,[4] nonmelanotic skin cancers,[5,6] psoriasis,[7] and macular degeneration,[8] with the use of systemic or topical photosensitizers. It has also been shown to be an effective therapy for the entire spec-

Author Affiliations: Division of Facial Plastic and Reconstructive Surgery, David Geffen School of Medicine at UCLA, Los Angeles, Calif. Dr Hall is now in private practice, Columbus, Ohio.

trum of actinic skin damage, from mild changes to premalignant AKs.[9,10] Cutaneous PDT protocols commonly use a topical photosensitizer precursor, 5-aminolevulinic acid (ALA), which is converted to the endogenous photosensitizer protoporphyrin IX by the heme biosynthetic pathway.[11] This conversion occurs selectively in the epidermis and active dermal appendages, ie, hair follicles and sebaceous glands. Radiofrequency (RF) energy is another nonablative medium that has recently been added to the armamentarium of the aesthetic specialist. It can achieve deep dermal tightening without epidermal damage as dermal tissues are heated to the point of collagen denaturation, resulting in an immediate tissue contraction and subsequent neocollagenesis.[12]

The combination therapy of IPL-PDT and RF energy takes advantage of 2 separate synergistic effects: synergy between PDT and RF-induced hyperthermia and between IPL and RF energy.

Multiple studies have shown increased tumor control with the combination of PDT and hyperthermia in mouse cancer models. The mechanism of this increase in tumor control is probably due to direct interaction of these modalities at the cellular level.[13-15]

The impedance of tissue is diminished when it is heated. Radiofrequency energy flows selectively to areas of diminished impedance. Intense pulsed light initially selectively heats a target lesion, allowing the secondary heating effect of RF to be compounded. The IPL is applied at a wavelength and pulse duration that are specific to the target lesion, followed by RF energy, which exponentially increases the temperature change initiated by the IPL.

The purpose of the present study was to determine the optimal duration of topical photosensitizer application (ALA) and IPL fluence levels for IPL-PDT and RF current in the treatment of photoaging in several skin phenotypes. We believe that this combination therapy, which allows the simultaneous treatment of both epidermal and dermal actinic changes, can achieve superior results without epidermal ablation. Knowledge of optimal treatment levels is a prerequisite to the development of safe and effective treatment protocols. Our treatment titration results have allowed us to develop 2 treatment protocols based on skin type and severity of actinic damage.

METHODS

We determined optimal treatment levels of IPL-PDT and RF energy for skin rejuvenation in patients with Fitzpatrick skin phenotypes I through III using 2 treatment end points: minimal erythema dose (**Figure 1**) and maximal tolerated dose. The 2 variables were time of application of 20% topical ALA (Levulan Kerastick; DUSA Pharmaceuticals Inc, Wilmington, Mass) and optical fluence of IPL. The RF energy was constant in all treatments at 20 J/cm^3. The epidermis was also cooled 5° to 20° before treatment.

Each patient was selected based on Fitzpatrick skin phenotype I, II, or III. All patients had no known history of photosensitivity or sensitivity to ALA. Treatment grids were drawn on both forearms of the subjects: 1 grid on each forearm for duplicate trials. Arms were shaved to allow full contact for skin treatment. Minimum fluence levels were selected based on the manufacturer's (Syneron Medical Ltd, Yokneam, Israel) guidelines for each skin type. Patients with Fitzpatrick types I and II skin were treated in 1 group at increasing fluence levels of 24, 26, 28, and 30 J/cm^2. Patients with Fitzpatrick type III skin were treated at 22, 24, 26, and 28 J/cm^2. The spectral range of the IPL was 580 to 980 nm. The ALA was applied in a single layer according to the manufacturer's instructions for periods of 30 minutes and 1, 2, and 3 hours. Each treatment group was assessed for erythema, subjective discomfort, and skin breakdown 1 hour after treatment. Both erythema and skin irritation (burning and pruritus) were rated as follows: 0, none; 1, mild; 2, moderate; 3, moderate/severe; or 4, severe. The subjects were followed up for 48 hours after treatment to determine if they had any epithelial breakdown or crusting (rated 0-4). Control treatments were completed at all fluence levels without ALA application.

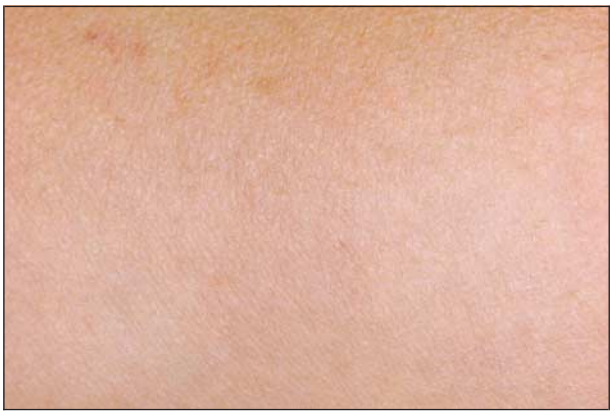

Figure 1. Erythema on forearm of a patient with Fitzpatrick type II skin after treatment with the minimal erythema dose of the combination of intense pulsed light–activated photodynamic therapy and radiofrequency energy at a fluence of 28 J/cm^2 and an aminolevulinic acid application time of 2 hours.

RESULTS

The results of the treatment trials are summarized in the **Table**. No patients of any skin type showed any effects with the control treatment (IPL and RF energy without ALA), even at maximum fluence levels. Treatment with ALA for 30 minutes also showed no effects in any patients at maximum fluence. The effects of ALA treatment became apparent after 1 hour at 28 and 26 J/cm^2 in Fitzpatrick types I/II and III, respectively. The first effects of treatment were mild erythema and mild discomfort consisting of a burning sensation and pruritus. These levels were determined to be our minimal erythema dose. As the duration of ALA treatment was increased to 2 and 3 hours, lower fluence levels resulted in greater erythema and discomfort. The maximum fluence levels in each group resulted in severe erythema at 2 and 3 hours of ALA treatment. The associated discomfort at these levels was rated as moderate/severe or severe. Epithelial crusting, which also occurred at the highest treatment levels, was rated as moderate or moderate/severe and healed without complications 7 to 10 days after treatment. These levels were determined to be the maximal tolerated dose. No treatment levels resulted in epithelial breakdown or blistering. The limiting factor to the use of higher energy levels and duration of ALA in this trial was patient discomfort, which was of comparable severity in each group at the 2 highest fluence levels at 2 and 3 hours of ALA treatment.

Table. Effects of Varying 20% Aminolevulinic Acid (ALA) Application Times and Intense Pulsed Light Fluence on Fitzpatrick Skin Types I/II and III*

Fluence, J/cm²	Effects	ALA Treatment Time				
		0 (Control)	30 min	1 h	2 h	3 h
Fitzpatrick I/II						
24	Erythema	0	0	0	0	0
	Discomfort	0	0	0	0	0
	Crusting	0	0	0	0	0
26	Erythema	0	0	0	1	1.5
	Discomfort	0	0	0	1	2
	Crusting	0	0	0	1	2
28	Erythema	0	0	1	3.5	4
	Discomfort	0	0	0	2	3
	Crusting	0	0	0	2	3
30	Erythema	0	0	1.5	4	4
	Discomfort	0	0	1	3	3.5
	Crusting	0	0	1	3	3
Fitzpatrick III						
22	Erythema	0	0	0	0	0
	Discomfort	0	0	0	0	0
	Crusting	0	0	0	0	0
24	Erythema	0	0	0	1	1
	Discomfort	0	0	0	2	2
	Crusting	0	0	0	1	2
26	Erythema	0	0	1	2	3
	Discomfort	0	0	1	3	4
	Crusting	0	0	0	2	3
28	Erythema	0	0	2	4	4
	Discomfort	0	0	2	3	4
	Crusting	0	0	1	3	3

*Radiofrequency energy is constant at 20 J/cm³. At 1 hour after treatment, erythema and patient discomfort (burning and pruritus) were rated as follows: 0, none; 1, mild; 2, moderate; 3, moderate/severe; or 4, severe. Epithelial crusting was similarly rated 48 hours after treatment. Controls were performed at all fluence levels without ALA application.

COMMENT

The basic principle of nonablative selective thermolysis of cutaneous vascular and pigmented lesions is based on the selective heating and destruction of the target lesion without damaging surrounding tissues. The common approach to achieving this selectivity has been to use lasers or IPL with wavelengths that are maximally absorbed by the target compared with adjacent tissues. A main limitation of these techniques is that the optical energy must pass through the epidermis to reach its target. This process may result in overheating of the epidermis, causing burn injury or pigmentation changes, especially in patients with dark skin.

The effects of PDT have been shown to be potentiated by concomitant tissue hyperthermia. Henderson et al[13] and Waldow et al[14,15] have published studies supporting this theory. Photodynamic therapy triggered by a variety of light sources in combination with microwave hyperthermia was shown to enhance tumor control in mouse mammary carcinoma and fibrosarcoma cell lines compared with PDT alone. The authors theorized that this synergy is achieved by a direct interaction of the cytocidal effects of the 2 modalities at the cellular level. The photorejuvenation combination therapy described herein may achieve superior clinical results from the synergy between PDT and RF-induced hyperthermia, causing increased destruction of dysplastic, photodamaged cells.

The concomitant use of IPL and RF energy takes advantage of a synergistic effect seen with these 2 technologies. This synergy is achieved because tissue at a higher temperature better conducts RF current, causing the tissue to be further heated compared with surrounding cooler tissue. The IPL initially selectively heats the target lesion and creates a temperature difference between the target lesion and the surrounding tissues. Target lesions with known absorption characteristics and thermal relaxation times can be selected by IPL being applied at a wavelength range and a pulse duration that are specific to them. The RF energy can then be applied to exponentially increase the temperature change initiated by the IPL. This method allows much lower fluence levels of optical energy to be used, which will spare the epidermis and surrounding tissues and result in a much safer and efficient way to target lesions. The system also protects the epidermis by precooling, which causes decreased conductivity of RF energy in the epidermis but does not affect the target lesion, further increasing the selectivity of the treatment. Low fluence levels of IPL that are safe for all skin types can be used in synergy with RF, which is not sensitive to skin pigmentation. We believe that the synergistic effects of the IPL-PDT and RF energy combination therapy will provide superior photorejuvenation results without epidermal ablation.

Photodynamic therapy involves the use of exogenous or endogenous photosensitizing molecules, which, when activated by light of a specific wavelength, mediate a reaction that yields cytotoxic oxygen singlets, resulting in cell destruction. It has been used to treat multiple epithelial diseases, including aerodigestive tract carcinoma, basal cell carcinoma, squamous cell carcinoma, and AKs, as well as all types of actinic skin damage. Aminolevulinic acid is a metabolic precursor to the endogenous photosensitizer protoporphyrin IX and is converted via the heme biosynthetic pathway that is present in all nucleated cells. Aminolevulinic acid–induced PpIX has been shown to accumulate preferentially in epithelial malignant and dysplastic premalignant cells compared with adjacent normal cells.[11] Photodynamic therapy with topical ALA therefore achieves selective therapeutic destruction of dysplastic cells in the epidermis and in epidermal appendages in the dermis (sebaceous glands and hair follicles). The most favorable absorption wavelengths of protoporphyrin IX (PpIX) are 410, 630, and 690 nm. Multiple activating light sources have been used with topical ALA, including unfiltered visible light, red noncoherent light, blue light, red laser light, and IPL. The use of IPL-induced PDT for photorejuvenation has been reported by Ruiz Rodriquez et al,[9] who applied ALA only to AK lesions, with the remaining areas of the face treated with IPL alone. The authors reported excellent results after 2 treatments at a 1-month interval without complications for treatment of all components of actinic damage, including AKs. The spectrum of IPL used in the present study was in the 580- to 980-nm range, which includes 2 absorption peaks for PpIX (630 and 690 nm).

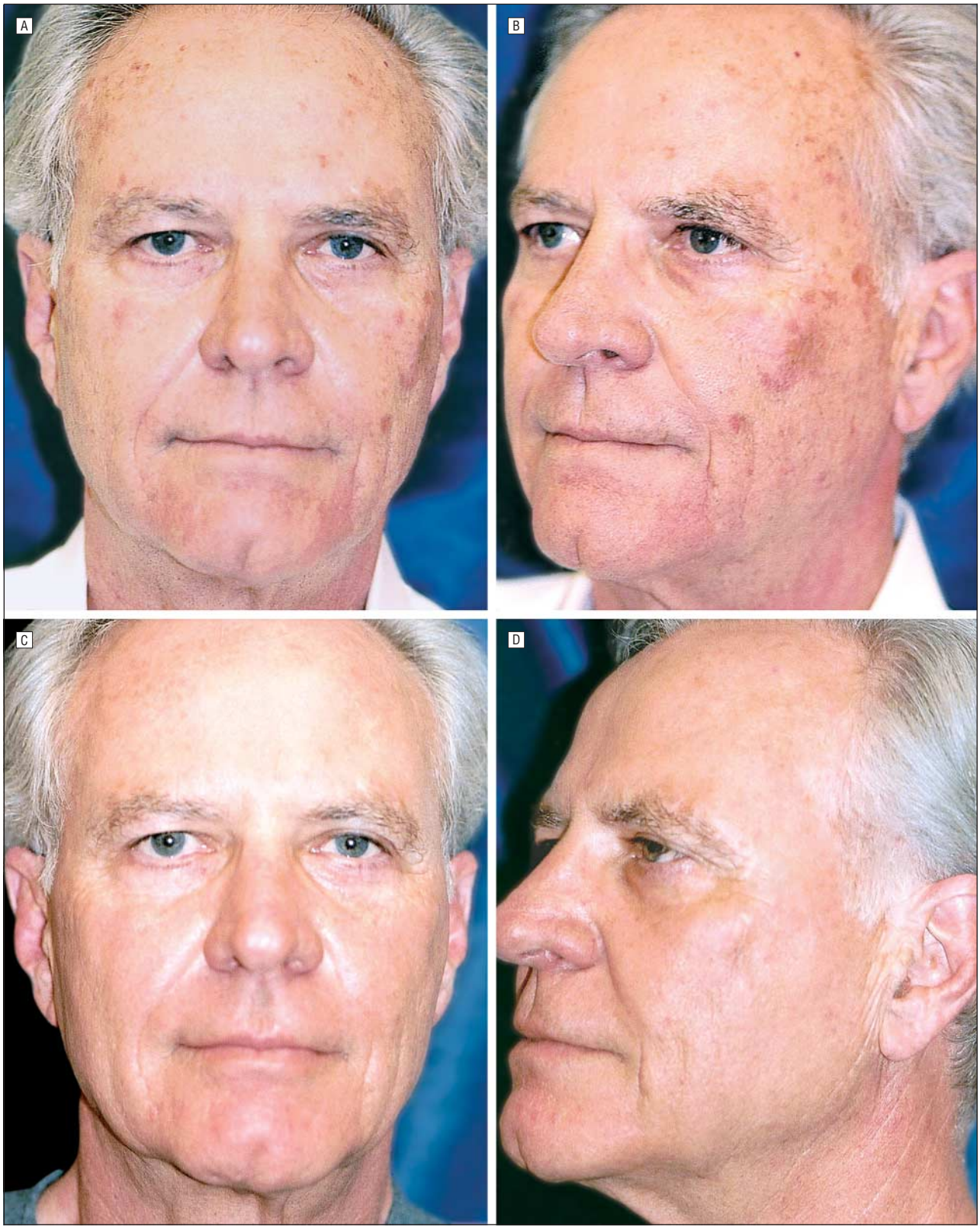

Figure 2. Preoperative (A and B) and postoperative (C and D) photographs of a patient who underwent 4 photorejuvenation treatments with the combination of intense pulsed light–activated photodynamic therapy and radiofrequency energy, with the first treatment consisting of a maximal tolerated dose or a "photopeel" treatment, followed by 3 "photofacial" treatments.

We believe that combination therapy using IPL-activated PDT enhanced with RF energy can offer excellent photorejuvenation results with simultaneous treatment of dermal and epidermal actinic changes (**Figure 2**). Topical ALA application time of 1 to 2 hours for all skin types and fluence levels of 26 to 28 J/cm^2 and 24 to 26

J/cm^2 for skin types I/II and III, respectively, were determined to be the minimal erythema dose. Topical ALA application times of 2 to 3 hours and fluence levels of 28 to 30 J/cm^2 and 26 to 28 J/cm^2 for skin types I/II and III, respectively, were determined to be the maximal tolerated dose, resulting in severe erythema and crusting but avoiding epidermal breakdown. The results of this dose-response study have allowed us to develop 2 treatment protocols based on skin type to treat mild and severe photodamage. Treatment for mild damage, or our photofacial protocol, requires fewer treatment sessions than IPL alone and uses treatment levels near the minimal erythema dose range. A more aggressive protocol, or photopeeling, uses levels near the maximal tolerated dose for severe photodamage with AKs. Photopeeling has a 5- to 7-day recovery period and appears to be better tolerated than fluorouracil treatment with shorter-term erythema and crusting. A patient series to critically evaluate the results of these protocols is in progress.

Accepted for Publication: July 27, 2004.
Correspondence: Gregory S. Keller, MD, 222 W Pueblo St, Santa Barbara, CA 93105 (faclft@aol.com).

REFERENCES

1. Weiss RA, Weiss MA, Beasley KL. Rejuvenation of photoaged skin: 5 years results with intense pulsed light of the face, neck, and chest. *Dermatol Surg*. 2002; 28:1115-1119.
2. Sadick NS. Update on non-ablative light therapy for rejuvenation: a review. *Lasers Surg Med*. 2003;32:120-128.
3. Bitter PH. Noninvasive rejuvenation of photodamaged skin using serial, full-face intense pulsed light treatments. *Dermatol Surg*. 2000;26:835-843.
4. Marcus SL, McIntyre WR. Photodynamic therapy systems and applications. *Expert Opin Emerg Drugs*. 2002;7:321-334.
5. Keller GS, Razum NJ, Doiron DR. Photodynamic therapy for nonmelanoma skin cancer. *Facial Plast Surg*. 1989;6:180-184.
6. Keller GS, Doiron DR, Fisher GU. Photodynamic therapy in otolaryngology–head and neck surgery. *Arch Otolaryngol*. 1985;111:758-761.
7. Szeimies RM, Calzavara-Pinton P, Karrer S, Ortel B, Landthaler M. Topical photodynamic therapy in dermatology [review]. *J Photochem Photobiol B*. 1996; 36:213-219.
8. Axer-Siegel R, Ehrlich R, Yassur Y, et al. Photodynamic therapy for age-related macular degeneration in a clinical setting: visual results and angiographic patterns. *Am J Ophthalmol*. 2004;137:258-264.
9. Ruiz-Rodriguez R, Sanz-Sanchez T, Cordoba S. Photodynamic photorejuvenation. *Dermatol Surg*. 2002;28:742-744.
10. Smith S, Piacquadio D, Morhenn V, Atkin D, Fitzpatrick R. Short incubation PDT versus 5-FU in treating actinic keratoses. *J Drugs Dermatol*. 2003;2:629-635.
11. Kennedy JC, Marcus SL, Pottier RH. Photodynamic therapy (PDT) and photodiagnosis (PD) using endogenous photosensitization induced by 5-aminolevulinic acid (ALA): mechanisms and clinical results [review]. *J Clin Laser Med Surg*. 1996;14:289-304.
12. Fitzpatrick R, Geronemus R, Goldberg D, Kaminer M, Kilmer S, Ruiz-Esparza J. Multicenter study of noninvasive radiofrequency for periorbital tissue tightening. *Lasers Surg Med*. 2003;33:232-242.
13. Henderson BW, Waldow SM, Potter WR, Dougherty TJ. Interaction of photodynamic therapy and hyperthermia: tumor response and cell survival studies after treatment of mice in vivo. *Cancer Res*. 1985;45:6071-6077.
14. Waldow SM, Henderson BW, Dougherty TJ. Potentiation of photodynamic therapy by heat: effect of sequence and time interval between treatments in vivo. *Lasers Surg Med*. 1985;5:83-94.
15. Waldow SM, Henderson BW, Dougherty TJ. Enhanced tumor control following sequential treatments of photodynamic therapy (PDT) and localized microwave hyperthermia in vivo. *Lasers Surg Med*. 1984;4:79-85.
16. Goldberg DJ, Cutler KB. Nonablative treatment of rhytids with intense pulsed light. *Lasers Surg Med*. 2000;26:196-200.