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Ablative Fractional Radiofrequency Combined with Sonophoresis Increases Skin Penetration of Indocyanine Green

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Dear Editor:

Indocyanine green (ICG) is a water-soluble tricarbocyanine dye with peak spectral absorption at 780 nm. Its intravenous application has been approved by the US Food and Drug Administration since 1959 for the determination of cardiac output, liver function diagnostics, and ophthalmic angiography[1-3].There are various reports of the use of ICG in dermatology, including contrast enhancement for *in vivo* epidermal and dermal structures visualized by fluorescence confocal microscopy[4], the treatment of mild to moderate acne[5], augmentation of therapeutic effect of diode lasers in port-wine stains, and photodynamic therapy for actinic keratosis[6].

Compared to conventional photosensitizers such as aminolevulinic acid (ALA) and methyl aminolevulinic acid (MAL), ICG is considered a good alternative because of its minimal side effects and fair therapeutic efficacy. Previous studies report the effect of ablative fractional laser for facilitating skin penetration of MAL and ALA according to the detection of increased porphyrin fluorescence[7-9]. Using ICG as a test drug, we measured immediate drug absorption assisted by ablative fractional radiofrequency (RF) combined with sonophoresis *ex vivo*.

Two male domestic Yorkshire swine (6～10 weeks old, 8～12 kg) were used. Skin tissue without subcutaneous fat was obtained from the flank area. For thawing, 3×3-cm^2 skin tissue cryosections were kept at 40°C for 1 hour and washed with saline. The experimental protocols were approved by the Kyung Hee University Animal institutional review board (KHMC-IACUC 11-028). Fractional ablative RF with the "RF Pixel" handpiece of the Legato system (Alma Lasers, Caesarea, Israel) was performed at 50 or 100 W, 40.68 MHz, and 15.4 ms pulse duration. A single-pass procedure was conducted without overlapping by using 6×50-pixel matrix on the tip. ICG cream (0.2%) was prepared by mixing ICG (Dongindang Pharm, Siheung, Korea) with petroleum jelly. The cream was applied at 0.3 g per 3×3 cm^2 skin to an approximate thickness of 1 mm. The ICG cream-treated areas were covered and occluded with aluminum foil to avoid light exposure. After ICG application, sonophoresis using the "IMPACT Pixel" handpiece of the Legato system (Alma Lasers) was performed

Table 1. Skin surface fluorescence intensities

Intervention	Skin surface fluorescence (AU)	
	RF 50 W	RF 100 W
Fractional RF + sonophoresis	5.6 (4.0～7.1)	6.3 (5.9～7.9)
Fractional RF + sonophoresis + ICG	14.0 (13.3～14.7)*	15.3 (13.2～16.1)*
ICG	7.2 (6.7～7.3)	
Untreated control	4.0 (3.9～4.1)	

Skin surface fluorescence intensities are shown in arbitrary units (AU) at different laser powers. Data were calibrated to a fluorescence standard ([intensity sample/intensity standard]×100) and are presented as median (interquartile ranges). RF: radiofrequency, ICG: indocyanine green. *Significantly higher intensity vs. corresponding ICG application without fractional RF and sonophoresis pre-treatment ($p<0.0001$).

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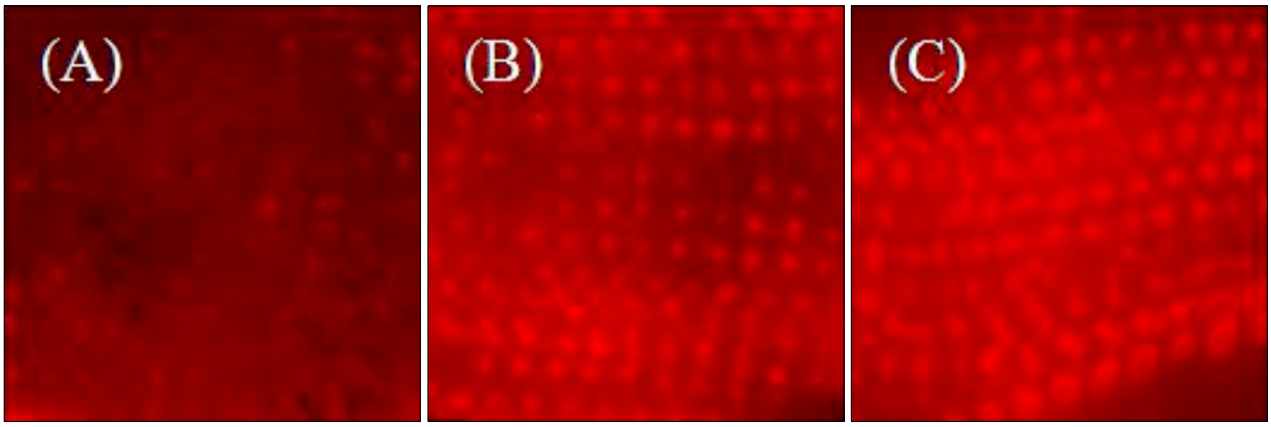

Fig. 1. Representative images showing skin surface fluorescence as a result of different treatments. (A) Without pretreatment, (B) pretreatment with fractional radiofrequency (RF)+sonophoresis at 50 W, (C) pretreatment with fractional RF+sonophoresis at 100 W.

with power of 50 Hz for 30 seconds. To detect and image ICG fluorescence, the Maestro system (Caliper Life Sciences Inc., Hopkinton, MA, USA) with a near-infrared 740 : 10 : 950 filter was used. The average fluorescence index was measured by the Maestro system immediately after treatment. Higher fluorescence intensity indicates greater percutaneous ICG uptake[8].

The results are summarized in Table 1. Fluorescence intensity was higher after fractional RF and sonophoresis without ICG application than that in the untreated control. It should be noted that when the dermal connective tissue is exposed after ablative treatment, the autofluorescence derived from collagen and elastin could increase the fluorescence intensity.

ICG-induced fluorescence was significantly higher on fractional RF and sonophoresis-pretreated skin than the untreated area ($p<0.0001$). Higher treatment energy tended to enhance fluorescence to a greater extent than lower energy, although the difference between energies was not significant (Fig. 1).

Fang et al.[7] report that among Er:YAG laser, microdermabrasion, iontophoresis, and electroporation, Er:YAG laser resulted in the greatest enhancement of ALA permeation. In addition, the addition of iontophoresis or electroporation toresurfacing techniques caused a profound synergistic effect on ALA permeation. Haedersdal et al.[8] report that ablative fractional laser treatment facilitates the delivery of topical MAL deep into the skin. Our results suggest ablative RF followed by sonophoresis can immediately double ICG fluorescence. Ablative RF using the Legato system uses RF energy to produce micro-sparks transmitted between the skin surface and RF electrode, producing micro-channels. Acoustic pressure ultrasound between the skin and sonotrode can enhance the delivery of ICG fluorescence via these micro-channels through a hammer-like "push-and-pull" effect. In a recent *in vivo* study using human skin, Issa et al.[10] demonstrated that pretreatment with ablative fractional RF associated with acoustic pressure improves the efficacy of steroids in hypertrophic scar treatment. Hence, it can be assumed that fractional laser and sonophoresis can be applied to enhance the absorption of intralesionally administered hydrophilic drugs.

The major limitation of the current study is that the test method was not compared with a previous method such as ablative laser or sonophoresis alone. In conclusion, fractional RF combined with sonophoresis pretreatment can facilitate the skin penetration of ICG. This pretreatment process can shorten the incubation period of ICG and maximize the treatment effect.

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A Case of Kaposi's Varicelliform Eruption in a Patient with Psoriasis Receiving Cyclosporine Therapy

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Dear Editor:

Kaposi's varicelliform eruption (KVE) is a disseminated cutaneous infection caused by several viruses such as herpes simplex virus (HSV) type 1 and 2, and coxsackievirus A16 in patients with an underlying dermatosis. The term "eczema herpeticum" is used when the pathogenic virus is HSV1 or HSV2. KVE may rarely occur in patients with psoriasis; "psoriasis herpeticum" refers to the occurrence of KVE in psoriasis patients[1,2]. Here, we report the case of patient with erythrodermic psoriasis who developed KVE while receiving cyclosporine therapy.

A 53-year-old male with a 30-year history of psoriasis vulgaris was admitted to our inpatient clinic with erythroderma starting 2 weeks earlier. Treatment with 4.5 $mg \cdot kg^{-1} \cdot day^{-1}$ cyclosporine A was initiated. On the 7th day of hospitalization, the patient developed vesicles and vesiculopustules all over the face, trunk, and extremities that progressed to papules with hemorrhagic crusts (Fig. 1, 2). A diagnosis of KVE was considered, and polymerase chain reaction (PCR) examination for HSV1 and HSV2 was performed; the result was positive for HSV1 infection. Bacterial culture from the lesions revealed no bacterial growth. Ocular investigation did not reveal a herpetic infection. Routine investigations including complete blood count, liver and renal function tests, and chest X-ray were normal. Therapy with intravenous acyclovir 10 mg/kg thrice daily was initiated and administered for 1 week. The lesions regressed completely within 10 days.

KVE is a potentially life-threatening viral infection that aris-

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