

ORIGINAL RESEARCH REPORT

## Skin rejuvenation by microneedle fractional radiofrequency and a human stem cell conditioned medium in Asian skin: a randomized controlled investigator blinded split-face study

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### Abstract

**Background and objectives:** For skin rejuvenation, microneedle fractional radiofrequency (RF) is a recently developed minimally invasive method for delivering RF energy directly into the skin using microneedle. Additionally, the use of growth factors in skin rejuvenation is emerging as a novel anti-aging treatment. We evaluated efficacy and safety of microneedle fractional RF for skin rejuvenation, and furthermore the synergistic effect of stem cell conditioned medium, composed of a large number of growth factors and cytokines. **Materials and methods:** Fifteen females were included for a split-face comparative study with a blinded response evaluation. One side of each subject's face was treated with fractional RF alone, and the other side was treated with fractional RF plus stem cell conditioned medium. Patients received 3 sessions of treatment at 4-week intervals. **Results:** All patients showed clinical improvement on physician's global assessment and patient satisfaction scores on both sides of their faces. Among objective biophysical measurements, improvement in hydration, melanin, erythema index and especially skin roughness was noticed. Stem cell conditioned medium provided a synergistic effect on improvement of skin roughness, which was statistically significant ( $p < 0.05$ ). Histologic examination revealed marked increase in dermal thickness and dermal collagen content. Side effects were minimal. **Conclusion:** Microneedle fractional RF is a safe and effective skin rejuvenation method, and the better results may be expected when combined with stem cell conditioned medium.

**Key Words:** aging, growth factor, microneedle fractional radiofrequency, stem cell conditioned medium

### Introduction

There are two biologically distinct aging processes affecting the skin. The one is intrinsic aging, which affects the skin by slow and irreversible tissue degeneration. The other is extrinsic aging, so called "photoaging" resulted from chronic ultraviolet (UV) exposure (1,2). Various energy-based modalities including lasers have been used to reverse symptoms of aging. Although ablative lasers are effective traditional treatment for photodamaged skin rejuvenation, they have significant side effects such as post-procedural erythema and postinflammatory hyperpigmentation, which occur more commonly in dark-skinned patients. Nonablative lasers are associated with less downtime, but the results seem to be limited and inconsistent (3–6). Recently, fractional radiofrequency (RF) has revolutionized

the field of skin rejuvenation. Hantash et al. (7) introduced a minimally invasive device, microneedle fractional RF, which adopted microneedle therapy system (MTS) for delivering bipolar RF energy directly into the skin through microneedle. RF thermal lesions are fractionally generated within the reticular dermis. Fractional thermal injury of deep dermal collagen induces a vigorous wound healing process leading to dermal remodeling and the generation of new collagen, elastin and hyaluronic acid (7–9). Moreover, microneedle fractional RF can provide a direct route for transdermal delivery of large hydrophilic molecules, such as growth factors, which are emerging as novel anti-aging treatments.

Growth factors may be beneficial in reducing signs of skin aging owing to their ability to promote dermal fibroblast and keratinocyte proliferation and

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to induce extracellular matrix formation including collagen (10). Endothelial precursor cells (EPCs) differentiated from human embryonic stem cell (hESC) demonstrated their effects on the improvement of blood perfusion in damaged tissues (11,12). Conditioned medium (CM) of hESC-derived EPC (hESC-EPC), which was composed of a large number of growth factors and cytokines, significantly improved signs of skin aging, and therefore could be one of the potential treatment options for skin rejuvenation.

The present 12-week randomized split-face study was undertaken to evaluate *in vivo* efficacy of microneedle fractional RF for skin rejuvenation in Asians, and furthermore the synergistic effect of stem cell conditioned medium (hESC-EPC CM) for skin rejuvenation. In particular, this study used histologic quantitative assessment and diverse non-invasive skin measuring devices to objectively assess changes in biophysical properties of skin following each treatment.

## Material and methods

### Patients

Fifteen patients were recruited for this prospective, randomized controlled, investigator-blinded, split-face study. All patients ranged in ages from 41 to 64 years (mean  $53.8 \pm 3.21$  years of age) and had skin type III and IV according to the Fitzpatrick scale. Exclusion criteria were: use of bleaching creams or history of any skin rejuvenation treatment within 6 months, history of keloid or active eczema. The study protocol and informed consent form were submitted and approved by the CHA University Institutional Review Board. All 15 patients were informed of the benefits, risks and possible complications of the treatment before enrollment, and informed consent was obtained from each patient.

### Description of devices

We used a microneedle fractional RF device (Scarlet<sup>TM</sup>, Viol Co., Korea), which had a disposable single-use treatment tip consisting of five non-insulated microneedle electrode pairs per the area of 10 mm<sup>2</sup>, with the exposed electrode extending from 0.5 to 3 mm below the skin surface. These bipolar electrode pins form a closed circuit through the irradiated skin, delivering 2 MHz of conducted RF current to the skin. Adjustable RF voltage up to a maximum of 40 V can be delivered, in relation to the intensity (1–10) and conduction time (100–800 ms).

### Preparation of conditioned media and multiplex cytokine assay

Conditioned medium (CM) of hESC-derived EPC (hESC-EPC) were generated as previously described

(12), which are now commercially available. The multiplex cytokine analysis of CM revealed that hESC-EPCs expressed significantly great amounts of several growth factors including epidermal growth factor (EGF), fibroblast growth factor-2 (FGF-2), fractalkine, granulocyte macrophage colony stimulating factor (GM-CSF), interleukin-6 (IL-6), platelet derived growth factor-AA (PDGFAA) and vascular endothelial growth factor (VEGF) (Table I).

### Experiment of cutaneous absorption

To confirm transdermal absorption, proteins in hESC-EPC CM were labeled with Alexa Flour 488 Protein Labeling Kit (Invitrogen Co., California, USA) according to the manufacturer's protocol. Female miniature pig skin (Medi kinetics micropigs<sup>®</sup>, Medi Kinetics Co., Ltd, Busan, Korea) was treated with a microneedle fractional RF device (Scarlet<sup>TM</sup>, Viol Co., Korea) with 1mm needle depth. Then, fluorescence dye-protein conjugates were applied on the skin and were incubated for 1 hour. Tissues were embedded immediately in frozen section compound (Leica Microsystems GmbH, Wetzlar, Germany) on liquid nitrogen. The slides were incubated with Fluoroshield<sup>TM</sup> Mounting Medium with DAPI (ImmunoBioScience Co., Washington, USA). Images were captured with Nikon fluorescence microscope (405 nm, 488 nm excitation) and were merged.

### Treatment protocols

Each patient's left and right side of the face was randomly assigned to either treatment with fractional RF alone or fractional RF plus hESC-EPC CM. The randomization procedure involved sealed

Table I. Multiplex cytokine analysis of secreted factors obtained from conditioned medium of hESC-EPCs.

	hESC-EPC (pg/ml)	EGM-2 (pg/ml)
EGF	10,168	9
FGF-2	421	61
Fractalkine	1,372	133
GM-CSF	689	313
IL-6	4,294	2463
IL-8	193,789	7
IL-9	302	9
IP-10	491	511
PDGF-AA	7,379	41
VEGF	4,092	42

EGF, epidermal growth factor; FGF-2, basic fibroblast growth factor; GM-CSF, granulocyte macrophage colony stimulating factor; IL-6, interleukin 6; IL-8, interleukin 8; IL-9, interleukin 9; IP-10, interferon-inducible protein-10; PDGF, platelet derived growth factor; VEGF, vascular endothelial growth factor. EGM-2 means the serum-free endothelial culture medium, which is used in culture of hESC-EPC, and used as a vehicle control medium in Milliplex analysis.

envelopes in which the allocation was indicated. The sealed envelopes were numbered from 1 to 15. The randomization was based on a digitally created random list (Graphpad Software Inc, La Jolla, CA) generated by an independent cooperator and envelopes were opened in ascending order. Patients and two dermatologists assessing outcomes were blinded until all the patients finished final assessments.

Patients received three treatments each spaced 4 weeks apart. Face was anesthetized using topical 4% lidocaine cream (LMX4, Ferndale Laboratories Inc., Ferndale, MI) about 30 minutes before the procedure. The face was cleansed with a mild soap and 70% alcohol. As per the manufacturer's recommendation, full face was treated with a microneedle fractional RF device (Scarlet™, Viol Co., Korea). The treatment parameters were determined based on the specific anatomical location and proximity of underlying bones. Treatment was delivered in a single, non-overlapping pass over the indicated area. An epidermal cooling device (CARESYS, Danil SMC, Korea) was used to relieve pain and erythema after the treatment. Postoperatively, 1.5 ml of normal saline was painted for the fractional RF alone treatment side, and 1.5 ml of hESC-EPC CM was painted for the fractional RF plus hESC-EPC CM treatment sides. Patients were instructed to avoid washing the face at least for 1 hour.

#### *Clinical assessments*

Patients were assessed at baseline and 4 weeks after the final treatment. Photographs by digital camera (Nikon D90, Tokyo, Japan) were obtained at each visit. For patients' self-assessment, patients answered questionnaires regarding efficacy and adverse events at 12 weeks after the commencement of the study. The patient satisfaction scale was as follows: 0 = not satisfied, 1 = somewhat satisfied, 2 = satisfied, 3 = very satisfied. In addition, patients were asked to report any adverse effects during the study. Objective clinical assessments were performed by two blinded dermatologists comparing before and after photos separately on each side of the face in non-chronological order. The two evaluators were not informed as to the study design. We used a quartile grading scale on the evaluations (grade 0 = no improvement; grade 1, 0–25% = minimal to no improvement; grade 2, 26–50% = moderate improvement; grade 3, 51–75% = marked improvement; and grade 4, 75–100% = near total improvement).

#### *Non-invasive objective skin hydration measurements*

Measurement of skin hydration was performed using a Corneometer CM825 (CK Electronics, Köln, Germany). The skin measurements were performed

at baseline and 4 weeks after the final treatment. Three corneometer readings were taken from the same malar areas and analysed to determine changes in skin hydration.

#### *Non-invasive objective skin color measurements*

Prior to all measurements, patients were acclimatized to the temperature (20°C)- and humidity(40%)-controlled room conditions and the instruments were calibrated according to the manufacturer's instructions. The narrow-band simple reflectance meter, Mexameter (MX18, Courage+Khazaka Electronic GmbH, Köln, Germany), was used to quantitatively evaluate color changes after treatments. This instrument uses arrays of light-emitting diodes that emit light at three defined wavelengths: 568 (green), 660 (red) and 880 (infrared) nm. Melanin index (MI) and erythema index (EI) were measured in triplicate on the same malar area on each side of the face and mean values were used for analysis.

#### *Non-invasive objective wrinkle measurements*

To evaluate the effects of treatments on collagen regeneration, each patient's periorbital wrinkles were objectively measured using skin replica and a microrelief instrument (Visiometer SV600, Courage+Khazaka Electronic GmbH, Köln, Germany) respectively, at 0 weeks and 4 weeks after final treatment. Visiometer can measure skin roughness and the depth of furrows by measuring the light transmission through a very thin skin replica. The roughness parameter investigated in this study was R2 (maximum roughness) and R3 (average roughness).

#### *Biopsy specimens and histologic measurements*

Biopsy specimens from 4mm-punch were obtained from each side of facial skin at baseline and at the end of treatment. Post-treatment biopsy specimens were taken near the previous biopsy site. Tissue samples were fixed in 10% buffered formalin, then embedded in paraffin. Standard hematoxylin-eosin and immunohistochemical staining, including procollagen-1 and fibrillin-1, were performed. Quantitative measurement of procollagen-1 was done using Image Pro software (version 7.0, Media Cybernetics, Bethesda, USA).

#### *Statistical analysis*

Paired T tests were carried out to compare interval changes in all parameters at each visit. Data were analyzed using SPSS software (version 12.0, SPSS Inc., Chicago, IL, USA). P values of less than 0.05 were considered statistically significant.

## Results

### Experiment of cutaneous absorption

The proteins in hESC-EPC CM labeled with Alexa Flour 488 Protein Labeling Kit were demonstrated both in the epidermis and the dermis after fractional RF treatment (Figure 1).

### Clinical assessments

All 15 volunteers completed the study. Final follow-up visit to our institute was scheduled at 4 weeks after the final treatment. All patients showed improvement of both skin laxity and pigmentation after microneedle fractional RF. Representative photographs showed more improvements of wrinkles and overall skin appearance following combined treatment of microneedle fractional RF and hESC-EPC CM than microneedle fractional RF only (Figure 2). Patients' overall satisfaction scores were  $2.00 \pm 0.65$  for fractional RF only and  $2.35 \pm 0.42$  for fractional RF plus hESC-EPC CM, respectively ( $p < 0.05$ , Table II). The mean degree of improvement in fine wrinkles and overall appearance determined by blinded investigator 4 weeks after the final treatment showed  $2.06 \pm 0.70$  for fractional RF only and  $2.20 \pm 0.68$  for fractional RF plus hESC-EPC CM ( $p < 0.05$ , Table II).

### Objective measurement of hydration improvement

At 4 weeks after the end of treatment, both sides of the patients' faces showed improvement in skin hydration score obtained by Corneometer, demonstrating the efficacy of fractional RF on skin hydration. Mean skin hydration of the sides treated with fractional RF and the others with fractional RF plus hESC-EPC CM increased from 46.18, 49.08 at baseline to 52.86, 55.11 at 2 weeks after the final session, respectively ( $p > 0.05$ , Figure 3A).

### Objective measurement of pigmentation improvement

At 4 weeks after the end of treatment, both sides resulted in decrease in the melanin index (MI) obtained by Mexameter, demonstrating the efficacy of fractional RF on skin lightening. Mean skin pigment of the sides treated with fractional RF and of the sides with fractional RF plus hESC-EPC CM decreased from 77.66, 79.11 at baseline to 72.26, 78.1 at 2 weeks after final session, respectively ( $p > 0.05$ , Figure 3B).

### Objective measurement of erythema improvement

At 4 weeks after the end of treatment, both sides resulted in decrease in the erythema index (EI) obtained by Mexameter. Mean EI of the fractional RF-treated side showed a decrease from 296.38 at

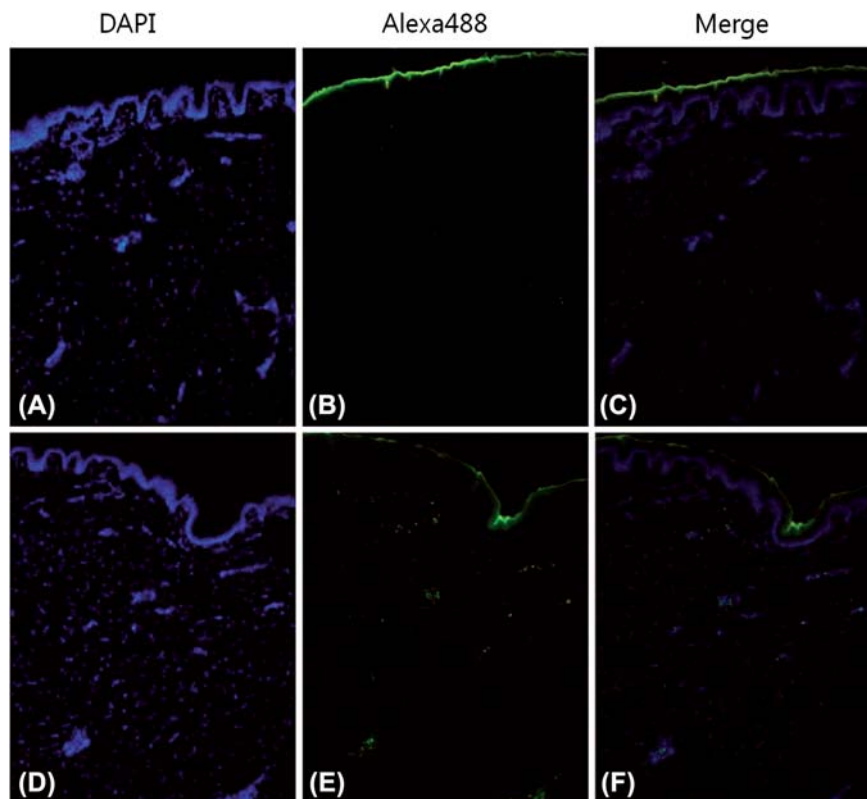


Figure 1. Transdermal penetration of hESC-EPC CM. (A–C) control, (D–F) fractional RF plus hESC-EPC CM. The proteins in hESC-EPC CM labeled with Alexa Flour 488 Protein Labeling Kit (green color) were demonstrated both in the epidermis and the dermis.



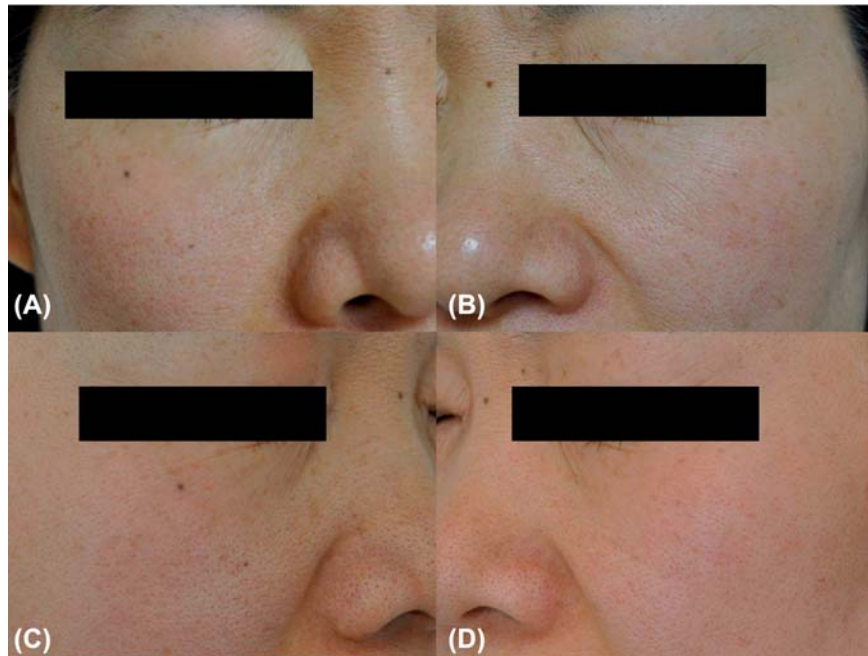


Figure 2. Representative clinical photographs. (A, B) baseline, (C) 4 weeks after the final treatment (fractional RF only), (D) 4 weeks after the final treatment (fractional RF + hESC-EPC CM).

baseline to 265.66 at 2 weeks after the final session ( $p > 0.05$ ) while Mean EI of fractional RF plus hESC-EPC CM-treated side significantly decreased from 297.11 to 265.66 ( $p < 0.05$ , Figure 3C).

#### Objective measurement of roughness improvement

At 4 weeks after the end of treatment, both sides resulted in a decrease in the R2 (Maximum roughness) and R3 (Average roughness) values measured by Visiometer. R2 and R3 values of the sides treated with fractional RF alone decreased from 1.00 and 0.63 at baseline to 0.85 and 0.55 at 2 weeks after the final session, respectively ( $p < 0.05$ ). Of note, there were greater reductions in R2 and R3 values of the fractional RF plus hESC-EPC CM-treated side between baseline (0.90, 0.56) and 2 weeks after final session (0.75, 0.43), respectively ( $p < 0.05$ ). hESC-EPC CM provided a synergistic effect to fractional RF on improvement of skin

roughness, which was statistically significant ( $p < 0.05$ , Figure 3D,E).

#### Histologic evaluation

Microscopic examination of hematoxylin-eosin stained sections showed dermal remodeling after microneedle fractional RF (Figure 4). A significant increase in dermal collagen content was observed at 4 weeks after 3 sessions of fractional RF (B) compared to baseline (A). More prominent increase in dermal collagen content was noted at 4 weeks after 3 sessions of fractional RF plus hESC-EPC conditioned medium (D) compared to baseline (C).

Immunohistochemical staining for fibrillin-1 revealed only scant fibrillin-rich microfibrils along the dermoepidermal junction (DEJ) before treatment. At 4 weeks posttreatment, staining for fibrillin-1 showed a significant increase in its density from DEJ to the deep dermis compared to the baseline (Figure 5).

Table II. Clinical assessments.

	Fractional RF only	Fractional RF plus hESC-EPC
Patient's overall satisfaction scores*	2.00 ± 0.65	2.35 ± 0.42
Blinded investigator evaluations†	2.06 ± 0.70	2.20 ± 0.68

\*Patient's overall satisfaction scores: 0 = not satisfied, 1 = somewhat satisfied, 2 = satisfied, 3 = very satisfied.

†Blinded investigator evaluations: grade 1, 0–25% = minimal to no improvement; grade 2, 26–50% = moderate improvement; grade 3, 51–75% = marked improvement; and grade 4, 75–100% = near total improvement.

#### Procollagen image analysis

Immunohistochemical staining for procollagen-1 revealed narrow collagen bands from the basement membrane to upper dermis (Figure 6). The density of procollagen-1 increased at 4 weeks after the final treatment. Quantitative assessment of the density of procollagen-1 within 0.2 and 0.5-mm depth of dermis from basement membrane showed significant increase at 4 weeks after 3 sessions of fractional RF compared to baseline ( $p < 0.05$ , Figure 7). More prominent increase in dermal

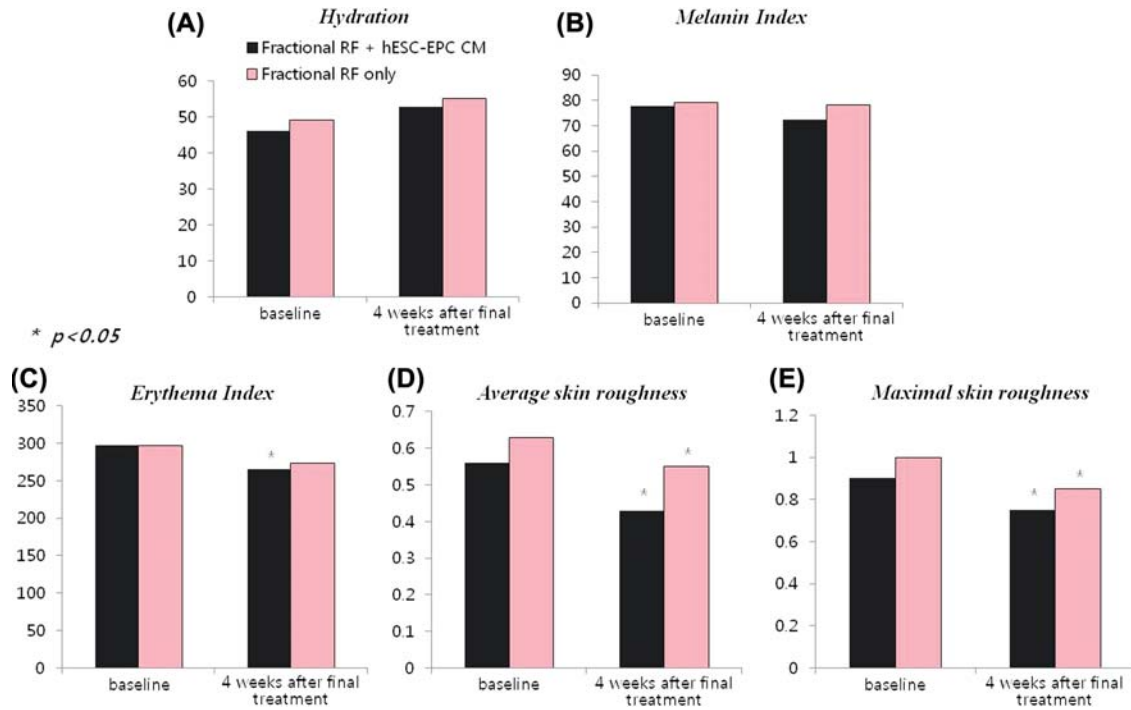


Figure 3. Skin measurements by non-invasive evaluation methods. (A) Objective measurement of hydration, (B) pigment, (C) erythema, and (D, E) wrinkles, (D) R3: average roughness, (E) R2: maximum roughness (E) (\* $p < 0.05$ ).

procollagen density was observed at 4 weeks after 3 sessions of fractional RF plus hESC-EPC-conditioned medium compared to the baseline ( $p < 0.05$ , Figure 7).

*Adverse events*

No serious adverse events were encountered. Mild pain and temporary erythema during and after procedures were well tolerated in all subjects. Other

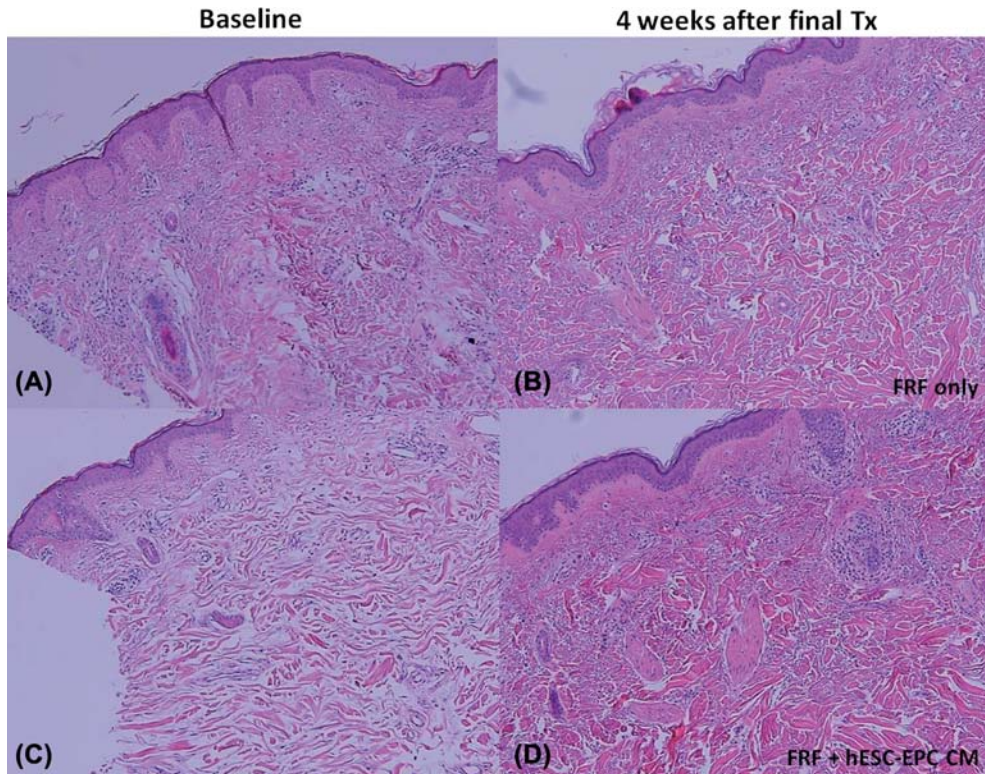


Figure 4. Dermal remodeling and neocollagenesis after microneedle fractional radiofrequency in H&E stain ( $\times 40$ ). (A, C) baseline, (B) 4 weeks after the final treatment (fractional RF only), (D) 4 weeks after the final treatment (fractional RF + hESC-EPC CM).



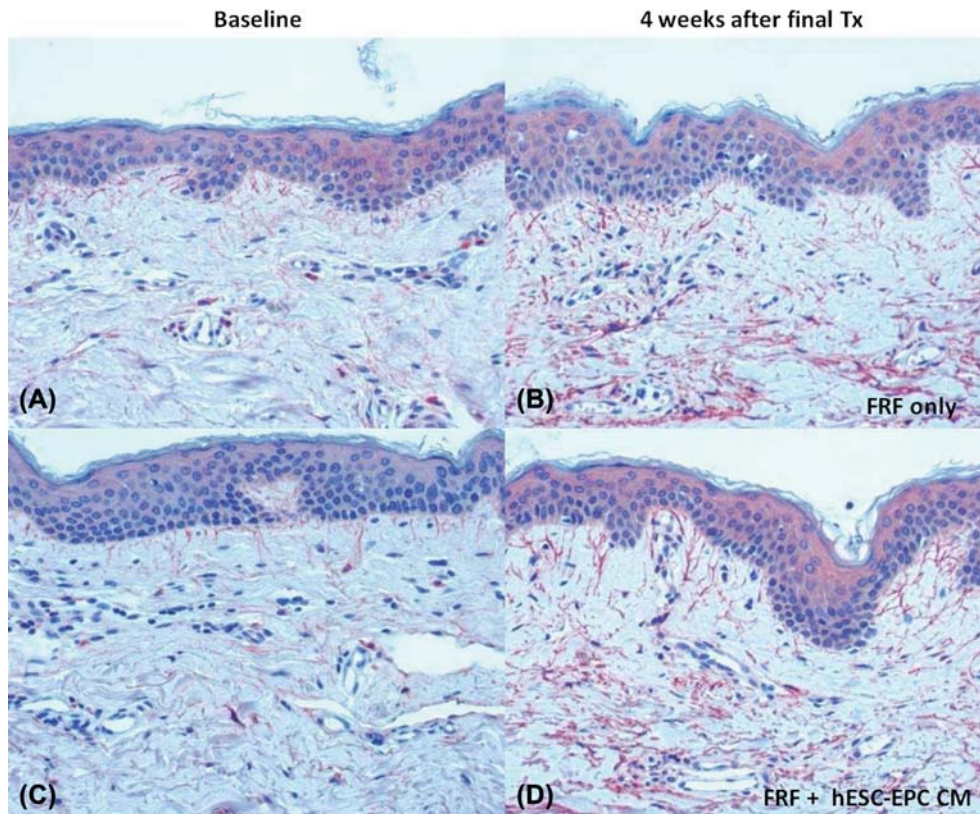


Figure 5. Immunohistochemical staining for fibrillin-1. (A, C) baseline, (B) 4 weeks after the final treatment (fractional RF only), (D) 4 weeks after the final treatment (fractional RF + hESC-EPC CM).

possible adverse events, including bruising, secondary infection, folliculitis, aggravation of erythema, scarring, and hyper/hypopigmentation, were not noted.

## Discussion

Skin aging is mediated by the effects of both natural aging process over time (intrinsic aging) and environmental factors (extrinsic aging) on its cellular and extra-cellular components. Although the treatment of photoaged skin has been focused on ablative laser resurfacing techniques, recently there is an increased interest in various nonablative techniques of skin aging, which enables skin rejuvenation with minimal downtime and complications (3–6). But post inflammatory hyperpigmentation was observed in up to 40% of those who received nonablative laser, especially in skin type III and IV (14).

RF is nonionizing electromagnetic radiation in the frequency range of 3 kHz to 300 GHz. In contrast to most lasers that target specific chromophores, RF is chromophore-independent and depends on electrical properties of target tissue. In 2008, FDA approved fractional RF to offer skin rejuvenation, which can achieve fractional and contiguous treatment patterns while sparing epidermis and key adnexal structures that contribute to rapid healing. Moreover, recently introduced microneedle fractional RF can control the depth of

RF thermal zones and can induce tissue heating focused on the dermis with lower risk of adverse events such as postinflammatory hyperpigmentation associated with epidermal injury. Unlike other microneedle fractional RF devices, Scarlet<sup>TM</sup> adopted non-insulated microneedle electrodes, which resulted in advantages regarding bleeding control during operation and broad electric field in the dermis. As the thermal effect from RF devices is related to the impedance and conductivity of skin, the energy impact around microneedle electrode is narrower at the epidermal surface and wider and deeper into the dermis, in contrast to previous laser-based fractional systems (16,17). In a study by Hruza and colleagues (18), subjects who received fractional RF treatments showed clinical improvement in skin texture by investigators' assessment, which was greater than 40%. In another study regarding facial photodamage in Asians, fractional RF treatments produced moderate (26–50%) and incremental improvements in skin smoothness and tightness (19). These results of previous studies in clinical improvement of overall skin appearance are comparable with those of this study, which shows 26–50% improvement over baseline. In particular, this is the first study using microneedle fractional RF, to our knowledge, which showed statistically significant improvement both in degree of skin roughness measured by Visiometer and histologic quantitative assessment of procollagen-1.

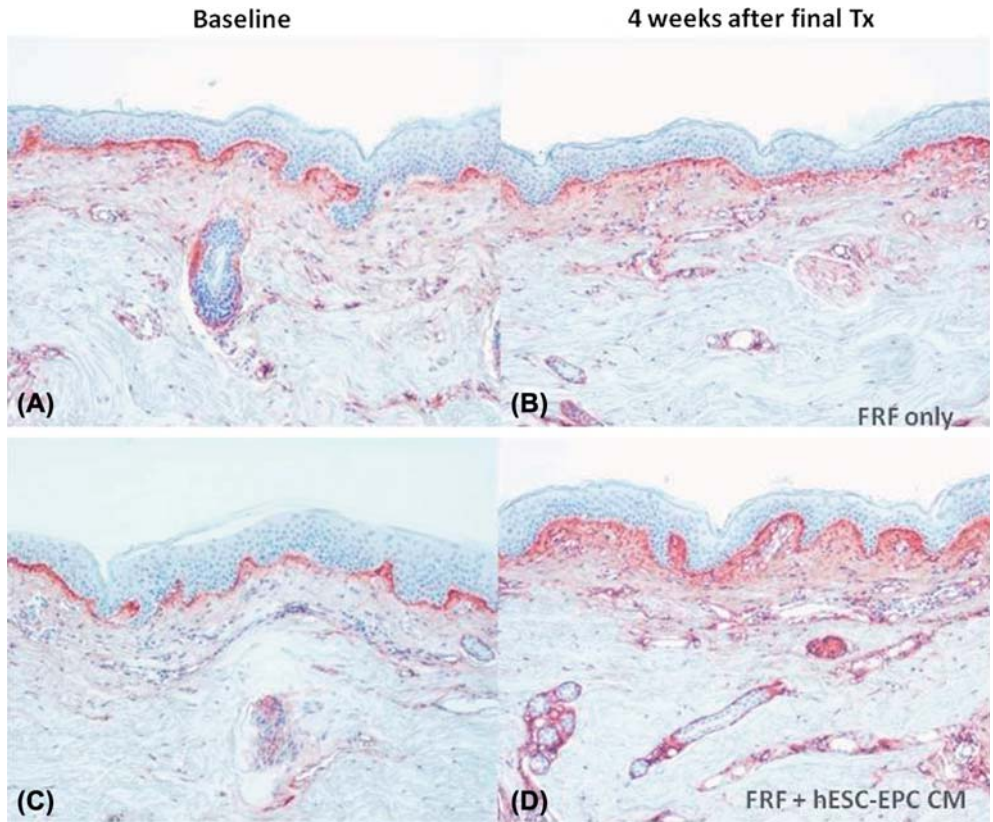


Figure 6. (A) Immunohistochemical staining for procollagen-1, (A, C) baseline, (B) 4 weeks after the final treatment (fractional RF only), (D) 4 weeks after the final treatment (fractional RF + hESC-EPC CM).

Adverse events found in the current study were limited to mild pain and temporary erythema during and after procedures. In general, incidence of side effects is lower with fractional RF than other non-ablative fractionated lasers. Some patients (up to 3–10%) may develop side effects such as depressions, vesiculations and superficial burn after conventional RF (6,14,16,20). These are mainly attributed to uneven electrode contact with the skin, which is sometimes unavoidable because of uneven facial contours (15). As microneedle fractional RF delivers

energy directly into the dermis, it may reduce the risk of adverse effects.

Additionally, secondary objective of this study was to evaluate the synergistic effect of stem cell (hESC-derived EPCs) CM when combined with microneedle fractional RF for skin rejuvenation. In vitro, hESC-EPC CM significantly improved the proliferation and migration of dermal fibroblasts and epidermal keratinocytes and also increased collagen synthesis of fibroblasts (12). Analysis of hESC-EPC CM with a multiplex cytokine array

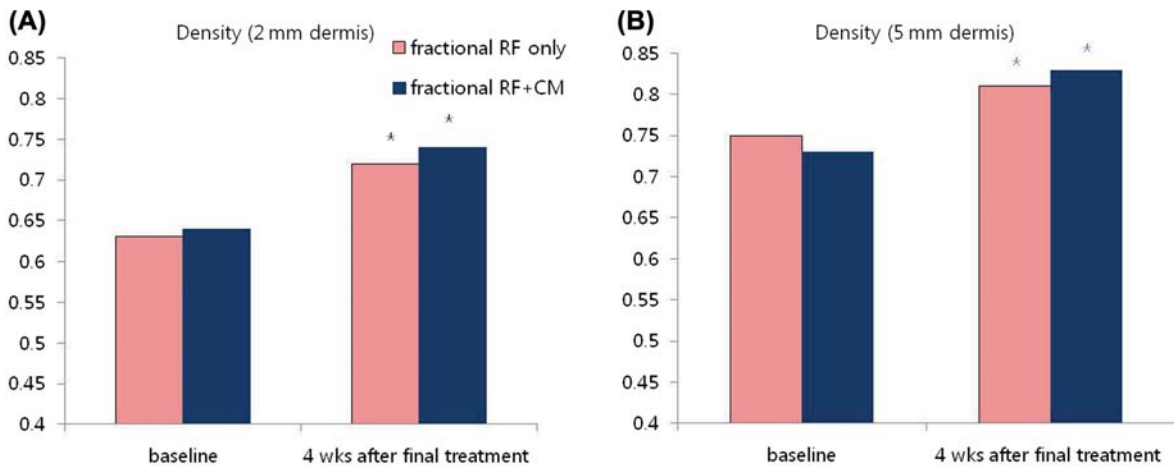


Figure 7. Quantitative assessment of the density of procollagen within 0.2 and 0.5 mm of dermis from basement membrane (\* $p < 0.05$ ).



system indicated that hESC-EPCs secrete cytokines and chemokines such as EGF, bFGF, fractalkine, GM-CSF, IL-6, IL-8, PDGF-AA and VEGF, which are well known to be important in normal angiogenesis and wound healing (12,13). It is well documented that hydrophilic molecules larger than 500 Dalton (Da) molecular weight have very low penetration through the stratum corneum. Most growth factors are large hydrophilic molecules greater than 20 kDa molecular weight; thus, penetration through the epidermis is an important matter to apply them for skin rejuvenation.

In this study, we conducted microneedle fractional RF to enhance skin penetration of hESC-EPC CM, which creates 300- $\mu$ m pin-hole wound. We confirmed that proteins in hESC-EPC CM could penetrate epidermis directly when combined with microneedle fractional RF. We could expect that the presence of hESC-EPC CM in the dermis show direct effects to dermal extracellular matrix and enhance wound healing following fractional RF. Our study demonstrated that combined treatment of microneedle fractional RF and hESC-EPC CM showed better results in patient satisfaction scores, investigator evaluations, skin roughness measured by Visiometer and histologic increase of collagen than microneedle fractional RF only treatment ( $p < 0.05$ ).

The main limitations of this study are the small number of patients and lack of long-term follow-up after final treatment. However, the randomized, face split-lesion design of this study enhanced the reliability of the data, as it enabled us to achieve significant results with a relatively small group of patients.

In conclusion, microneedle fractional RF is safe and effective treatment in Asian for skin rejuvenation, and combined treatment of microneedle RF and stem cell conditioned medium showed a synergistic effect on skin rejuvenation.

**Declaration of interest:** The authors state no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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