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Combination of Fractional Microneedling Radiofrequency and Ablative Fractional Laser versus Ablative Fractional Laser Alone for Acne and Acne Scars

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Purpose: Fractional microneedle radiofrequency (FMR) systems are used to treat inflammatory acne and scarring. Nonetheless, few controlled studies have combined this treatment with the traditional ablative fractional laser (AFL). We aimed to assess the safety and efficacy of the combination of FMR and AFL versus AFL alone in treating acne and acne scars.
Materials and Methods: In this 20-week, randomized, split-face study, 23 Korean patients with facial acne and acne scars underwent FMR and AFL treatments. One half of each patient's face was randomly assigned to receive FMR+AFL, whereas the other half received AFL alone. Treatments were administered in three consecutive sessions at 4-week intervals. This study investigated the severity of inflammatory acne, acne scars, individual lesion counts, depressed scar volumes, as well as patient and physician satisfaction. In addition, five patients underwent skin biopsy, and sebum output was measured.
Results: The FMR+AFL treatment demonstrated superior efficacy compared to AFL alone in terms of inflammatory acne and acne scar grading, lesion counts, and subjective satisfaction. The side effects were minimal and well-tolerated in both groups. Immunohistochemical findings from skin biopsy samples revealed that the application of FMR+AFL could induce an inhibitory effect on sebum secretion at the molecular level.
Conclusion: FMR combined with AFL is a well-tolerated and effective treatment modality for inflammatory acne and acne scarring.

Key Words: Acne vulgaris treatment, acne vulgaris scars, ablative fractional laser, fractional microneedle radiofrequency therapy

INTRODUCTION

Despite recent advances in pharmacological and non-pharmacological treatments for acne and acne scars, the treatment of these conditions remains challenging. Various non-pharmacological modalities for acne and acne scars have been introduced, with variable efficacy and safety profiles.[1-4] Among these options, ablative fractional lasers (AFL) can induce re-epithelialization and neocollagenesis in atrophic scars by inducing microthermal zones.[5] However, a substantial recovery time is required, and there is a potential risk of post-inflammatory hyperpigmentation, hypertrophic scarring, and infection.[6]

Fractional microneedle radiofrequency (FMR) devices transfer radiofrequency energy directly to the deep dermal structure with minimal epidermal injury, by conducting an electrical current through an array of microneedles.[7-9] Previous studies have shown that FMR can be combined with other laser modalities, such as AFL and pulsed dye lasers, to treat inflammatory acne and acne scars with favorable efficacy and safety profiles.[10-13]

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Through a prospective, split-face, randomized comparison study, we aimed to investigate the effectiveness of concurrent FMR+AFL versus AFL alone in treating acne and acne scars.

MATERIALS AND METHODS

Clinical study design and patients

The present study was designed to have a 20-week, prospective, randomized, single-blinded and split-face protocol, to compare two facial sides, either receiving FMR+AFL or AFL alone, for inflammatory acne and acne scars. Twenty-five adults exhibiting both inflammatory acne and acne scars for more than 6 months were eligible for the study. The exclusion criteria were a history of keloid scarring, pregnancy, mental illness, history of chemical peeling, plastic surgery, or laser treatment during the previous 6 months. In addition, participants who had consumed oral isotretinoin or other oral and topical anti-acne medications within the previous 3 months were excluded from the study, and study participants were not allowed to use any systemic, topical, or energy-based acne treatment during the study period.

A random number generator was used to generate zeroes and ones, using Microsoft Excel (2019 version; Microsoft, Redmond, WA, USA), to assign the treatment modality to each side. Each random assignment code was sealed separately in a nontransparent envelope until all data analyses were completed. The study duration was 20 weeks and included three consecutive treatment sessions at 4-week intervals (weeks 0, 4, and 8) and two follow-up assessment visits (weeks 12 and 20) after the final third treatment (Supplementary Fig. 1, only online). The Institutional Review Board of our institution approved this study (IRB No. 1-2020-0046) in compliance with the ethical principles of the Declaration of Helsinki, and informed consent was obtained from each participant.

Treatment protocols and devices

A dual-wave mode (pulsed/continuous) FMR, consisting of the handheld applicator with a disposable tip, which comprises minimally invasive non-insulated microneedles arranged in 1.5-mm spacing, 5×5 arrays (Sylfirm X, Viol Co., Ltd., Seongnam, Korea), and ablative fractional carbon dioxide laser with a 10600-nm wavelength (eCO_2, Lutronic Co., Goyang, Korea) were used in this study. All laser treatments were performed by a single experienced dermatologist at the specialized scar laser clinic of a tertiary referral center (JMK).

After gentle cleansing of the skin, 2.5% topical lidocaine hydrochloride and 2.5% topical prilocaine cream were applied under occlusion 30 min before laser treatment. FMR was performed on one side of the face, which was chosen by random assignment, and treatment parameters were adjusted as follows: pulsed-wave mode (PW4), 1.6–2.0 mm microneedle depth, intensity level ranging from 4 to 6, and one pass with <20% overlap. Consecutively, one pass of AFL to both sides of the face was delivered with 100 mJ and a density of 100 spots/cm^2, which correlates to 15.6% coverage and an ablation depth of 1168 μm.

Assessment of treatment efficacy

The primary efficacy endpoints included assessment of the severity of inflammatory acne and acne scarring. Two blinded board-certified dermatologists (JHL and YIL) evaluated the hemi-modified Global Acne Grading Score (hemi-mGAGs)[14] and Scar Global Assessment (SGA)[15] scale by comparing digital photographs in a non-chronological order (Supplementary Table 1, only online). In addition, an artificial intelligence-assisted labeling program (Ululab Inc., Seoul, Korea) automatically counted individual lesions (inflammatory lesions: papules, pustules, and nodules; non-inflammatory lesions: open and closed comedones). The depression mode of the three-dimensional skin analysis camera system (Antera 3D, Miravex, Dublin, Ireland) was adopted to assess the depressed volume of post-acne scar quantitatively. Additionally, we assessed the participants' and investigators' satisfaction with treatment outcomes using the Global Aesthetic Improvement Scale (GAIS), a five-point scale (0=worse, 1=no change, 2=improved, 3= much improved, and 4=very much improved).

Skin biopsy, immunohistochemistry staining, and measurement of sebum secretion

Five participants volunteered and provided informed consent for sequential skin biopsies during the study. Skin biopsies were performed at baseline (week 0) and 12 weeks after the final treatment (week 20). Two 3-mm skin tissue specimens were obtained from both sides of the midpoint between the tip of the chin and the mandibular angle. Moreover, to measure the sebum output level, sebum was collected from each adjacent site of the skin biopsy by applying the Sebumeter SM 8155 (Courage Khazaka electronic, Köln, Germany).

The 4-μm thick slides were prepared and used for immunohistochemistry staining, according to the standard experimental protocol. Briefly, the tissues obtained from skin biopsies were fixed in 10% formalin and embedded in paraffin. The samples were cut 4-μm thick and fixed on slides. For antigen unmasking, the sections were boiled for 30 min. After incubation with 3% hydrogen peroxide for 10 min, slides were blocked for 1 h at room temperature. With the primary antibodies (FoxOA1; 1:250, ab52857, Abcam, Cambridge, UK; PPAR-gamma; 1:500, MA5-14889, Invitrogen, Waltham, MA, USA), the slides were incubated overnight at 4°C. Detection was performed using a peroxidase/3,3'-Diaminobenzidine detection kit (K5007; DAKO, Carpinteria, CA, USA) and Mayer's hematoxylin (s3309; DAKO). All immunostained sections were visualized under a light microscope (BX43F, Olympus, Shinjuku, Japan), and the dye intensity of the stained area was measured using an image analysis program (ImageJ, MATHWORKS, Inc., Natick, MA, USA) at a magnification of × 400.

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Safety assessment

We performed a visual inspection and physical examination to assess the safety of the procedures at each visit. In addition, participant reports on the type and severity of treatment-related adverse events (e.g., hyper- or hypopigmentation, pinpoint bleeding, bruising, and scarring) were documented.

Statistical analysis

Data are presented as numbers (percentages) or means±standard deviations, according to the type of data. For time-dependent between-group comparisons, repeated-measures analysis of variance (RM-ANOVA) and subsequent post-hoc analysis using Student's t-test with Bonferroni correction were performed to compare and incorporate the parameters at each time point. A linear-by-linear association test was used when the categorical variables were in ordered categorical 2xN tables. A *p*-value <0.05 was considered statistically significant. All statistical analyses were performed using SPSS, version 25.0 (IBM Corp., Armonk, NY, USA).

RESULTS

Patient characteristics

A total of 25 Korean patients with both inflammatory and acne scars were enrolled from April 8, 2021, to December 7, 2021. The average age of patients was 24.1±4.76 (range, 19–36) years, and 16 patients (64.0%) were male. The Fitzpatrick skin types ranged from III to IV. Two participants dropped out due to withdrawal of consent; in the end, 23 completed the 20-week follow-up period. The per-protocol analysis was conducted on data obtained from the 23 participants.

Acne grading scores and lesion counts

In the RM-ANOVA and subsequent post-hoc analysis, there was no difference in the hemi-mGAGs at baseline between the FMR+AFL and AFL sides (34.1±9.00 vs. 32.9±8.43, $p>0.05$), whereas the FMR+AFL group showed a significant decrease in the hemi-mGAGs compared to the AFL group ($p<0.001$) (Fig. 1A). For all types of acne lesion counts (total, inflammatory, and non-inflammatory), the FMR+AFL group showed a significantly higher reduction than the AFL group after receiving the second session (Fig. 1B–D). In the RM-ANOVA, the lesion

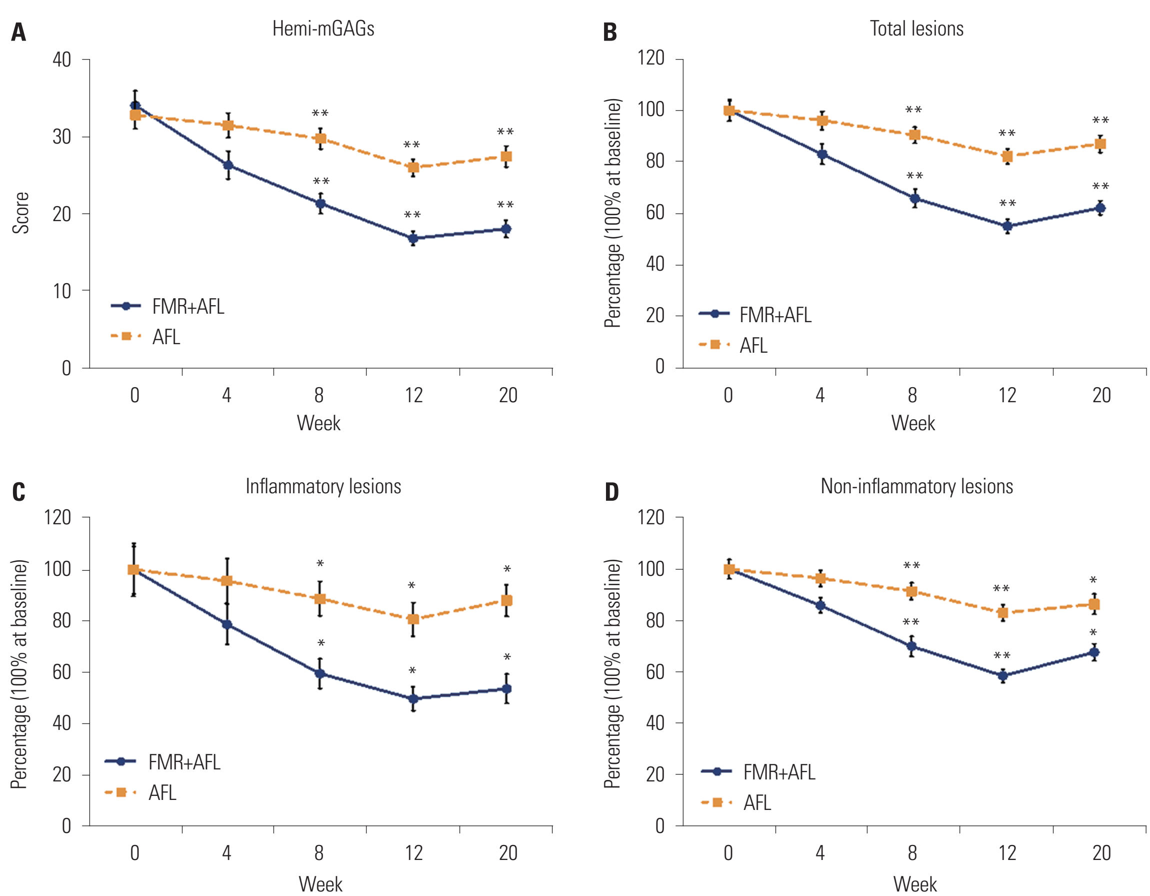

Fig. 1. Changes in acne severity levels by time and the treatment group, (A) measured by the hemi-modified Global Acne Grading Score (hemi-mGAGs), percent changes of (B) total acne lesion counts, (C) inflammatory lesion counts, and (D) non-inflammatory lesion counts during the study period. *$p<0.05$, **$p<0.001$ in post-hoc analysis with Bonferroni correction at each time point. AFL, ablative fractional laser; FMR, fractional microneedle radiofrequency.

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count had a significant effect on the interaction between time and group allocation ($p<0.001$). At the final 20-week follow-up visit, the inflammatory counts decreased by 46.3% (from 20.1 to 10.8) on the FMR+AFL side and by 12.0% (from 18.9 to 16.7) on the AFL side ($p=0.005$). Non-inflammatory lesion counts were reduced by 32.3% (from 30.8 to 20.8) on the FMR+AFL side and by 13.6% (from 30.7 to 26.5) on the AFL side ($p=0.005$).

Acne scar scale and depressed scar volume

The mean SGA scale scores of baseline (week 0), week 12, and week 20 on the AFL group were 2.13±0.69, 1.57±0.84, and 1.74±0.75, respectively. For the FMR+AFL side, the SGA scale scores of these time points were 2.26±0.62, 1.39±0.78, and 1.26±0.69, respectively. RM-ANOVA, considering the time-group interaction, showed significant differences between the FMR+AFL and AFL groups ($p=0.004$), and post-hoc analysis revealed a significant reduction in the SGA scale score in the FMR+AFL group compared to that in the AFL group at week 20 ($p=0.03$). Quantitative analysis using the depression mode of Antera 3D (Miravex) showed that the depressed volume by post-acne scar changed from 8.09±5.41 mm^3 (baseline) to 6.33±3.36 mm^3 (week 20) on the FMR+AFL side and from 7.96±5.15 mm^3 (baseline) to 7.69±4.79 mm^3 (week 20) on the AFL side. Significant differences between the two groups were noted by RM-ANOVA ($p=0.048$), yet they failed to reach significance for specific time points in the post-hoc analysis (Fig. 2).

Participant and investigator satisfaction

After the 20-week study period, 82.6% of the patients rated the treatment outcome as much improved or very much improved, based on the GAIS for the FMR+AFL treatment, whereas 60.9% of the participants rated the treatment outcome as much improved or very much improved for the AFL treatment. Investigators stated that 91.3% of the FMR+AFL side was much improved or very much improved, whereas 17.9% of the AFL side were rated the same (Fig. 3). A linear-by-linear association test revealed that an increasing trend in the GAIS score was significantly associated with the FMR+AFL side compared with the

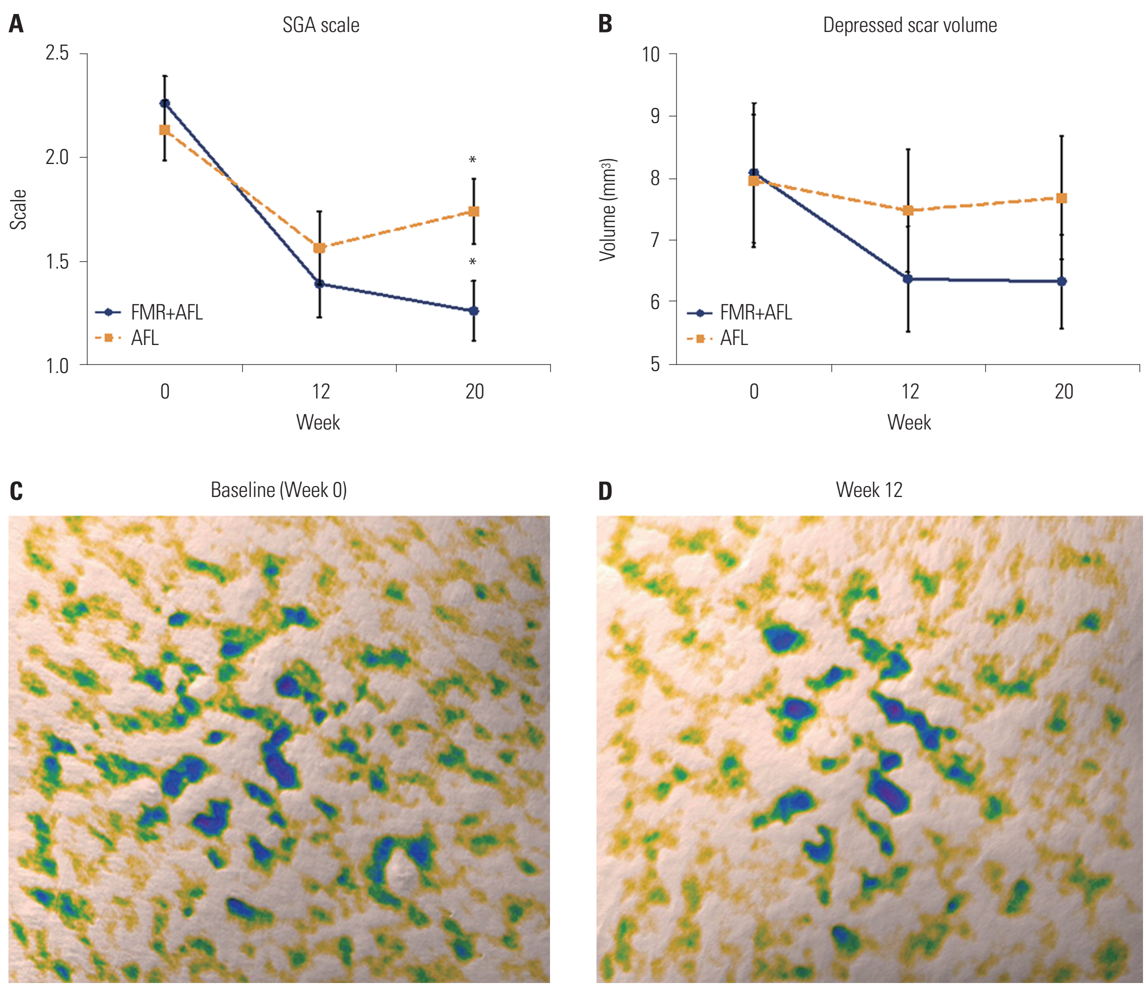

Fig. 2. Changes in acne scar severity by time and the treatment group, (A) measured by the Scar Global Assessment (SGA) scale and (B) changes in the depressed volume of the scar during the study period. Images of the depression mode captured using the Antera 3D camera system (C) before the treatment (baseline), and (D) after three sessions of FMR+AFL treatment. *$p<0.05$ in post-hoc analysis with Bonferroni correction at each time point. AFL, ablative fractional laser; FMR, fractional microneedle radiofrequency.

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AFL side, both for those provided by the participants (p=0.021) and investigators (p<0.001). Examples of the participants' before and after images are displayed in Fig. 4.

Immunohistochemical staining and sebum secretion measurement

Biopsy samples obtained from the five volunteers underwent

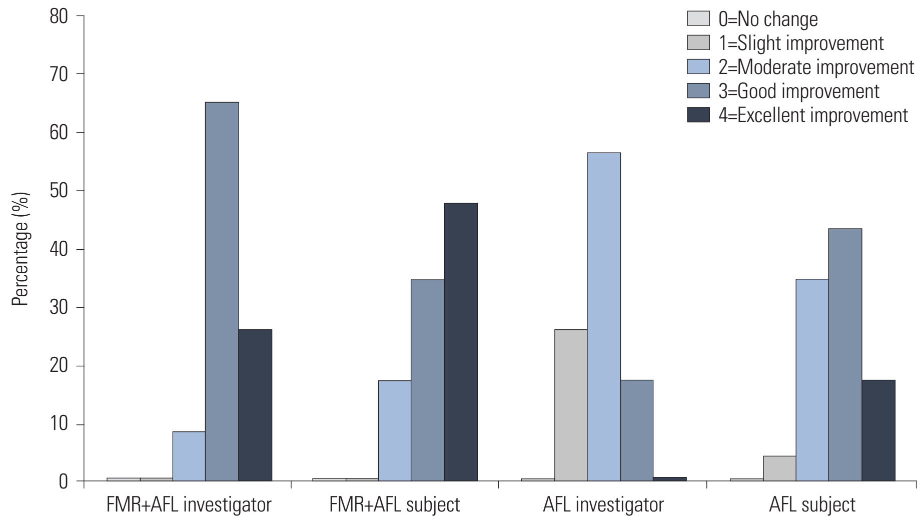

Fig. 3. Subjective participants' and investigators' satisfaction with treatment outcome assessed using the Global Aesthetic Improvement Scale. AFL, ablative fractional laser; FMR, fractional microneedle radiofrequency.

Fig. 4. Clinical representative photographs of the FMR+AFL and AFL sides at baseline and week 12 in the same patient. Improvements in acne and acne scars were noted on both sides; however, the degree of improvement was higher on the FMR+AFL side. AFL, ablative fractional laser; FMR, fractional microneedle radiofrequency.

immunohistochemical staining with FoxO1A and PPAR-γ (Fig. 5A–D). The nuclear-to-cytoplasmic ratio of FoxO1A immunostaining intensity was calculated and compared between the time points and treatment groups. Nucleo-cytoplasmic ratio of the FMR+AFL group at baseline was 0.162±0.011, and it significantly increased to 0.371±0.022 at week 20 (p<0.001). Similarly, staining ratio in the AFL group increased from 0.163±0.011 (at baseline) to 0.298±0.017 (at week 20; p<0.001). Nucleus/cytoplasm ratio at week 20 was significantly higher in the FMR+AFL group than in the AFL group (p<0.001). Immunohistochemical nuclear staining of the PPAR-γ yielded similar trends as those of the nucleo-cytoplasmic ratio of FoxO1A; staining intensity of PPAR-γ was increased at week 20 both in the FMR+AFL and AFL groups compared to that at baseline (p<0.001). In addition, staining intensity at week 20 was significantly higher in the FMR+AFL group than in the AFL group (p<0.05). On the FMR+AFL side, sebum secretion at baseline was 83.3±14.4 μg/cm^2, and it significantly reduced to 72.9±20.7 μg/cm^2 after 20 weeks (p<0.05). Conversely, on the AFL side, sebum secretion slightly increased at week 20 (93.3±40.1 μg/cm^2) compared to that at baseline (81.9±14.4 μg/cm^2); however, this difference failed to reach statistical significance (Fig. 5E).

Safety assessment

Most participants reported transient erythema, edema, and crusting after the procedure, which were well-tolerated and resolved within hours to a few days. No significant difference was observed in the frequency of posttreatment erythema and edema between the two sides (data not shown). Serious treatment-related adverse effects, such as scarring, bleeding, pigmentary alterations, and secondary infections, were not observed during the study period.

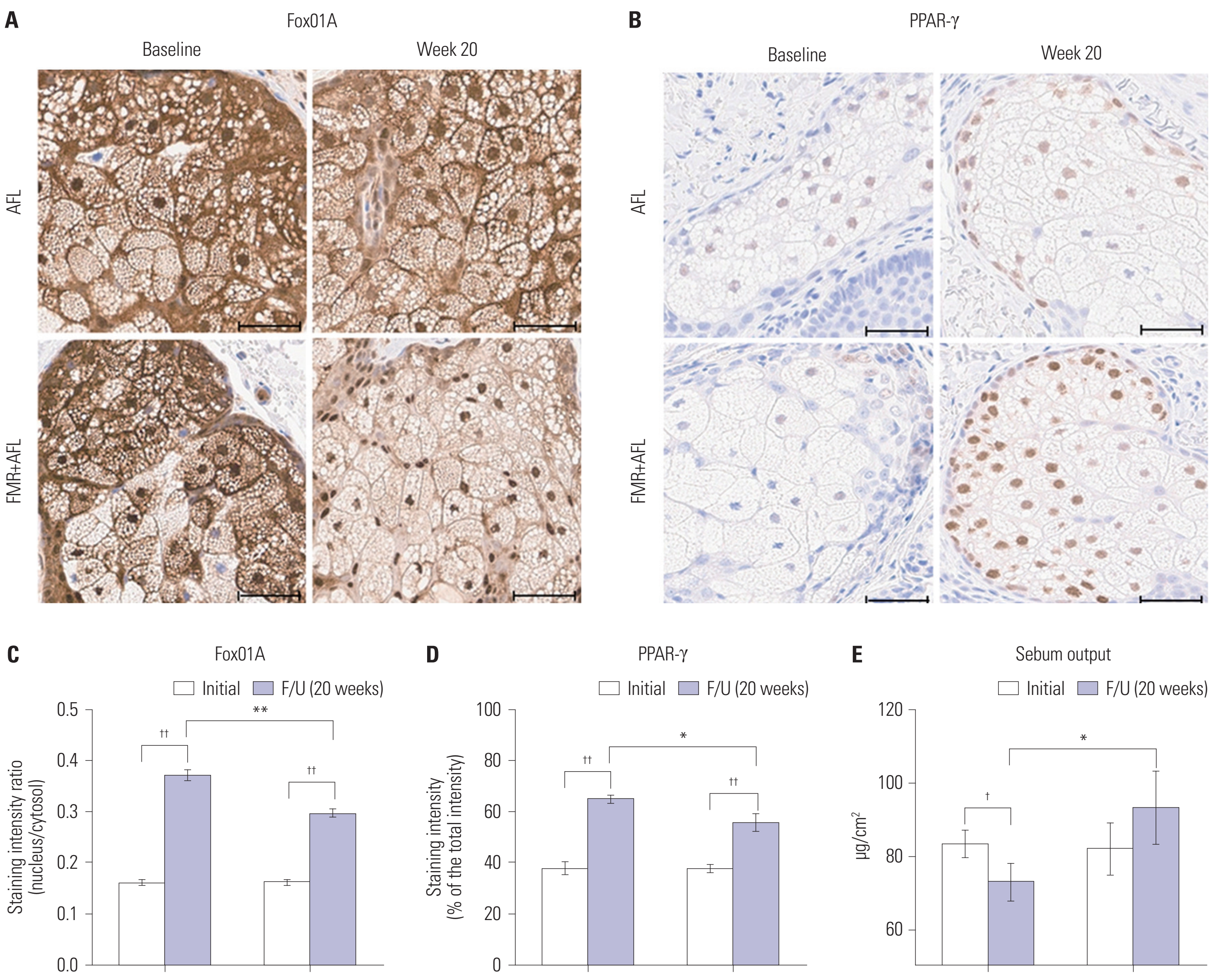

Fig. 5. Characteristic immunohistochemical staining images for (A) FoxO1A and (B) PPAR-γ according to the treatment group and time point. (C) Nucleo-cytoplasmic ratio of FoxO1A staining intensity, (D) staining intensity of PPAR-γ expression, and (E) sebum output level measured using Sebumeter. Scale bar=100 μm. *p<0.05, **p<0.001, Mann-Whitney U test, and †p<0.05, ††p<0.001, Wilcoxon signed-rank test. AFL, ablative fractional laser; FMR, fractional microneedle radiofrequency; FoxO1A, forkhead box-O1A; PPAR-γ, peroxisome proliferator-activated receptor-gamma.

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DISCUSSION

This prospective, split-face, single-blind, randomized controlled study suggested that the concurrent use of FMR and AFL is more effective than AFL monotherapy in treating acne and acne scars. This study also found that the combination of FMR and AFL resulted in a significant improvement in the severity of inflammatory acne and acne scarring, as measured by the hemi-mGAGs, lesion counts, and SGA scale. The participants and investigators reported higher levels of satisfaction with the FMR+AFL treatment outcomes than with AFL outcomes. Furthermore, skin biopsy results showed that the concurrent use of FMR and AFL affected the regulation of sebum production at the molecular level.

Several studies have assessed the safety and effectiveness of the combination of FMR and AFL for treating acne scarring, all of which showed a significant reduction in acne scar severity scores with acceptable safety profiles.[2,10,12,13] Meanwhile, several studies have reported improvements in inflammatory acne assessed by acne severity scoring or lesion counts with FMR treatment.[8,11] In our study, the FMR+AFL treatment demonstrated superior efficacy compared to AFL monotherapy in patients with both inflammatory acne and post-acne scars. The gap in improvement rate for inflammatory acne and acne scars between the two methods was more prominent in the follow-up period (Figs. 1C and 2A); sustained improvement for up to 2 months indicated the potential advantages of FMR, such as its protective effects against acne recurrence or scar formation.[8]

Microneedling devices have been reported to improve scarring and skin texture by inducing microscopic epidermal perforations and stimulating the migration or proliferation of keratinocytes and fibroblasts.[16,17] When coupled with pulsed bipolar RF, alternating high-frequency electrical currents at close intervals provide sufficient energy to the surrounding tissues to promote dermal neocollagenesis and elastogenesis without damaging the epidermis.[18-20] In this study, face sides allocated to the FMR+AFL group received FMR treatment immediately, followed by AFL on the FMR-treated area. We expected this combination treatment to have a synergistic effect on the treatment of post-acne scars. First, RF microneedling induces mechanical disruption of dermal fibrotic strands and collagen remodeling; subsequently, AFL irradiation causes epidermal resurfacing by controlled tissue vaporization on the demarcated scar margins.[2,12,21]

Previous studies have revealed decreased sebum output and reduced sebaceous glands after fractional RF treatment, which may be the mechanisms that result in the clinical improvement of inflammatory acne.[8,19,22] In our study, the FMR+AFL treatment induced an increase in the nucleocytoplasmic ratio of FoxO1A in vivo, which is known to be closely related to the pathogenesis of acne. FoxO1 is a key "nutrient-sensing" transcription factor that modulates the expression of genes involved in sebocyte apoptosis, lipid metabolism, oxidative stress, and immune functions.[23,24] The nuclear translocation of FoxO1 activates sestrin 3 expression, which, via activation of adenosine monophosphate-responsive protein kinase, inhibits mTORC1 signaling, sebaceous lipogenesis, and pro-survival signaling.[23,25] Skin expression of FoxO1 was mainly in the cytoplasm in untreated patients with acne, whereas oral isotretinoin intake increased the nuclear expression levels of FoxO1, which were similar to the results of the FMR+AFL group in this study.[25,26]

Along with the expression levels of FoxO1, those of PPAR-γ were also increased by FMR+AFL treatment. Although the role of PPAR-γ in the lipogenic pathway is complex and depends on the specific ligand–receptor interactions, several studies suggested decreased PPAR-γ expression levels in sebocytes in patients with acne or in acne-induced animal models.[27-29] In a previous study, the protein levels of Nuclear factor-kappa B (NF-κB) and IL-8 were found to be downregulated at the FMR-treated site in comparison to the non-treated site.[30] Considering our current findings, it is plausible to suggest that the increased expression of PPAR-γ might be attributed to the downregulation of NF-κB. Consequently, the elevated PPAR-γ expression could lead to a reduction in IL-8 expression. This interplay between increased PPAR-γ expression and reduced inflammation could potentially indicate a therapeutic effect on acne. Furthermore, a combination treatment of RF and intense pulsed light on an acne-induced rabbit ear model showed increased PPAR-γ expression levels, similar to the findings of this study.[27]

The present study had some limitations. First, it included a relatively small sample, with identical ethnic backgrounds and similar Fitzpatrick skin types. Thus, further studies are needed to confirm the efficacy and safety profile of the FMR+AFL treatment, particularly for darker skin types. Second, there are multiple confounding factors related to sebum secretion, such as weather changes, diet, and anatomical location of the measurement.[23,31,32] Third, the assessment of the participants' satisfaction was not blinded. This could potentially introduce bias in how participants responded, as their knowledge of the treatment they received might influence their reported satisfaction. Another limitation is the potentially reduced efficacy of the AFL treatment in treating acne scars. This may be attributed to our study's focus on patients with skin of color, leading us to use a relatively low fluence, low-density AFL protocol to minimize the risk of post-inflammatory hyperpigmentation.[2,33] Additionally, our study aimed to simultaneously treat both acne scars and inflammatory acne lesions. This dual focus might have dispersed the laser's energy density, potentially affecting the improvement rate in acne scars. Finally, the study was conducted during the coronavirus disease 2019 era, during which all participants wore disposable personal protective equipment, such as surgical masks or N95 respirators. Among them, 13 patients were classified into the "maskne" group, which was defined as patients with worsening of pre-existing acne on the mask-covered area after wearing masks for at least

6 h/day.[34-36] In the post-hoc subgroup analysis, patients in the maskne group showed a lower response to treatment than those in the non-maskne group (Supplementary Fig. 2, only online). Microbial dysbiosis induced by increased moisture and skin temperatures from fabric masks may influence the therapeutic response; however, further studies are warranted to elucidate these phenomena.[36]

In conclusion, the combination of FMR and AFL appears to be an effective and safe treatment choice for patients with inflammatory acne and acne scarring. We have previously reported the real-world practice of the combined use of low-dose isotretinoin and different modes of energy-based interventions.[11] As the FMR+AFL treatment showed inhibitory effect on sebum secretion, reduced acne lesions, and improved scar texture, it can be considered a promising treatment option for personalized medicine, with or without pharmacological interventions.

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The study device (Sylfirm X; Viol Co., Ltd., Seongnam, Korea) was provided by Viol Co. Viol had no role in the study design, implementation, data collection, data analysis, data interpretation, manuscript preparation, manuscript review, or manuscript approval.

AUTHOR CONTRIBUTIONS

Conceptualization: Jemin Kim, Sang Gyu Lee, Young In Lee, and Joohee Lee. Data curation: Jemin Kim, Sang Gyu Lee, Young In Lee, and Jihee Kim. Formal analysis: Jemin Kim, Sang Gyu Lee, Joohee Lee, and Jihee Kim. Funding acquisition: Jemin Kim, Jihee Kim, and Ju Hee Lee. Investigation: Jemin Kim, Sang Gyu Lee, Sooyeon Choi, and Young In Lee. Methodology: Sooyeon Choi, Young In Lee, Joohee Lee, and Jihee Kim. Project administration: Jemin Kim, Jihee Kim, and Ju Hee Lee. Resources: Jemin Kim and Sooyeon Choi. Software: Jemin Kim and Sang Gyu Lee. Supervision: Ju Hee Lee. Validation: Jemin Kim, Sang Gyu Lee, and Ju Hee Lee. Visualization: Jemin Kim and Sang Gyu Lee. Writing—original draft: Jemin Kim and Sang Gyu Lee. Writing—review & editing: Jemin Kim, Sang Gyu Lee, and Ju Hee Lee. Approval of final manuscript: all authors.

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