Safety of Combined Fractional Microneedle Radiofrequency and CO_2 as an Early Intervention for Inflammatory Acne and Scarring Treated With Concomitant Isotretinoin

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BACKGROUND Fractional microneedle radiofrequency (FMRF) systems are popular options for treating acne scars. However, treatment efficacy when used in combination with traditional ablative fractional laser (AFL) and the safety profile with concomitant use of isotretinoin remain unknown.

OBJECTIVE The aim of this study was to assess the safety and efficacy of an early intervention combination treatment protocol for inflammatory acne and acne scars.

MATERIALS AND METHODS The electronic records of 71 patients with inflammatory acne and acne scars were included in this retrospective observational study. Data were collected for all patients who received combination FMRF and AFL. Within the study group, 43 patients were receiving low-dose isotretinoin or had completed isotretinoin within the past 3 weeks.

RESULTS The mean Scar Global Assessment score significantly decreased after 3 sessions of combination treatment ($n = 71$). Patients with inflammatory acne showed a significant decrease in the number of inflammatory lesions ($n = 30$). Patients with concomitant low-dose isotretinoin use reported a further decrease in Scar Global Assessment score ($n = 43$). There were no reported persistent side effects, including prolonged inflammatory reaction or scarring.

CONCLUSION Combination treatment with FMRF and AFL is an effective and well-tolerated treatment modality for acne scars and inflammatory acne.

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Inflammatory acne and acne scars are often perceived negatively by society and can cause a significant adverse psychosocial impact.[1] Atrophic scars are the most common type, representing 80% to 90% of acne scars. Atrophic scars can be stratified as icepick, boxcar, or rolling based on morphologic features.[2] In a recent epidemiologic study, 43% to 69% of patients presenting with inflammatory acne had scarring.[3] Although current systemic treatments may improve active inflammatory lesions, they cannot normalize established atrophic acne scars. Acne scar treatment remains a therapeutic challenge with a broad range of treatment options available, including surgical modalities, chemical peels, lasers, and energy-based devices. Fractional lasers may induce neocollagenesis in atrophic scars, and ablative fractional laser (AFL) systems demonstrate efficacy in multiple studies.[4] However, to achieve sufficient resurfacing, AFL carries a significant risk of postinflammatory hyperpigmentation, scarring, infection, and substantial downtime.[5] When treating patients with darker skin types (Fitzpatrick III or

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more), laser irradiation density should be adjusted to prevent undesirable events.[6]

Radiofrequency (RF) devices use electromagnetic radiation to generate an electric current that heats the dermis, causing neocollagenesis. Fractional microneedle RF (FMRF) consists of the application of bipolar RF to the skin by microneedles to create columns of thermal damage.[7,8] As a result, controlled dermal collagen contraction can be achieved with minimal epidermal injury. Fractional microneedle RF is a popular approach for treating atrophic acne scars.[8,9] Moreover, RF devices are actively used in combination with other laser systems, such as non-AFLs.[10]

The use of isotretinoin during laser- or energy-based intervention for acne scars remains controversial. Classic guidelines often recommend avoiding invasive procedures for at least 6 months after the last dose due to the risk of delayed wound healing or abnormal scarring.[11] Recent studies suggest that laser treatment is safe when conducted within 1 to 3 months of systemic isotretinoin treatment.[12,13] Isotretinoin is usually administered to achieve therapeutic doses over a span of months to years. Thus, for patients with a high risk of severe acne scarring, it would be desirable to consider intervention while the patients are still undergoing systemic isotretinoin treatment. Despite the popularity of energy-based device (EBD), especially FMRF, the safety profile remains unknown with recent discontinuation or concomitant use of isotretinoin.

Here, the authors analyzed the efficacy of combination treatment with FMRF and AFL for acne scars and inflammatory acne. In addition, the authors assessed the safety of combination treatment in patients receiving systemic isotretinoin to address the efficacy of early intervention for acne scars.

Materials and Methods

Study Design and Participant Selection

In this retrospective observational study, the electronic patient medical records at Severance Hospital, Yonsei University Health System in Seoul, Korea, were searched to identify all patients who underwent fractional needle RF between January 1, 2015, and December 31, 2017. The end date was selected to ensure at least 3 months of follow-up after the patient received treatment. The study was approved by the Yonsei University Ethical Review Board (Study no; 4-2017-1227).

Inclusion criteria were patients older than 18 years with clinically diagnosed acne, acne scars, and treatment with combination FMRF and AFL.

Intervention

Laser Treatment

Patients underwent combination treatment with FMRF using a ScarLet (Viol, Sungnam, Korea) device followed by ablative fractional CO_2 with a 10,600-nm eCO_2^{TM} (Lutronic Co., Goyang, Korea). Topical 2.5% lidocaine HCl and 2.5% prilocaine cream were applied under occlusion 1 hour before treatment. Treatment parameters were as follows. The intensity of the RF device was set to 8 of 10 with a density of 25 microscopic treatment zone (MTZ)/cm^2 and depth of 2.0 to 2.8 mm. The energy of fractional CO_2 was set to

TABLE 1. Scar Global Assessment Scale

Category	*Score*	*Description*
Clear	0	No visible scars from acne
Almost clear	1	Hardly visible scars from 50 cm away
Mild	2	Easily recognizable: less than 50% face area
Moderate	3	50%–75% face area involved
Severe	4	>75% face area involved

Adapted from Dreno et al.[15]

TABLE 2. Grade of Acne Severity

Level of Disease	*Score*	*Inflammatory Lesion Count (Papules and Pustules) per Half Face*
Mild	1	0–5
Moderate	2	6–20
Severe	3	21–50
Very severe	4	>50

Adapted from Tan et al.[16]

100 mJ with a density of 100 spots/cm^2, which correlates with 15.6% coverage and an ablation depth of 1,168 μm. Eyelids and perioral areas were not treated. During the study, patients who were taking systemic isotretinoin maintained their dosage, and topical agents containing retinoic acid derivatives were prohibited.

Assessment

Efficacy end points included assessment of the severity of acne scarring and inflammatory lesion count. Objective assessments of clinical improvement were made by 2 independent dermatologists (J.M.K. and Y.I.L.) based on digital photographs. The Scar Global Assessment (SGA) scale[14] and Grade of Acne Severity[15] were developed and validated in previous publications and were used as outlined in Tables 1 and 2, respectively.

Textural improvement before and after treatment were compared by a global improvement scoring system (grade 0 = worse; grade 1, 1%–25% = minimal improvement or steady state; grade 2, 26%–50% = moderate improvement; grade 3, 51%–75% = marked improvement; and grade 4, >75% = near-total improvement).

Statistical Analysis

Treatment-related adverse effects, including persistent erythema, hyperpigmentation, scarring, and infection were assessed based on photographs and medical records. Data acquired by clinician assessments were compared using the *t*-test or Wilcoxon signed-rank test and the Mann–Whitney *U* test. The differences were considered significant if $p < .05$. All statistical analyses were performed using SPSS version 23.0 (SPSS Inc., Chicago, IL).

Results

Demographics

Seventy-one patients (33 men and 38 women) were enrolled in the study. The mean age was 24.8 years (range, 19–38 years), and Fitzpatrick skin types ranged from II to IV (13 patients had type II, 40 patients had type III, and 18 patients had type IV). On the initial physical examination, 43 patients had inflammatory lesions, and the remaining 28 patients had scars only (Table 3). All patients were Korean. Treatment history for acne and scarring included systemic or topical retinoids, topical or systemic tetracycline/minocycline, ablative or nonablative lasers, and intralesional triamcinolone injection (Figure 1).

Efficacy of the Combination Treatment Fractional Microneedle Radiofrequency and Ablative Fractional Laser

Treatments were performed every 4 to 6 weeks, and the average number of treatments was 3.31 sessions. To evaluate treatment efficacy, masked assessment of digital photography was performed with 71 patients who received more than 3 sessions. The mean SGA score was 3.14 ± 0.76 at baseline. The SGA score was significantly decreased at 1.58 ± 0.70 after 3 sessions of treatments ($n = 71$, $p < .05$, *t*-test) (Table 4). The grade of acne severity[15] was assessed for the 30 patients who had >5 active inflammatory lesions (papules or pustules). At baseline, the score was 2.63 ± 0.81, which decreased to 1.2 ± 0.41 after 3 sessions, representing a significant decrease in the number of inflammatory lesions ($n = 30$, $p < .05$, Wilcoxon signed-rank test) (Figure 2).

TABLE 3. Subject Demographics

Demographics	*Total*
Total no. of patients	71
Males, *n* (%)	33 (46.48)
Females, *n* (%)	38 (53.52)
Mean age (mean, SD)	24.8 ± 5.0
Fitzpatrick skin type, *n* (%)	
II	13 (18.31)
III	40 (56.34)
IV	18 (25.35)
Clinical characteristics	
Inflammatory acne†	30 (40.25)
Acne scar‡	41 (57.75)
Concomitant treatment, *n* (%)	
Systemic isotretinoin*	43 (60.56)

*Systemic isotretinoin-treated group includes any patients who had concomitant treatment with isotretinoin during the energy-based device intervention and those who discontinues within 3 weeks.

†"Inflammatory Acne" group includes patients with more than 5 active lesions (papules, pustules, or nodules) on half of the face.

‡"Acne Scar" group includes patients with mainly atrophic acne scars and less than 5 active lesions indicated above.

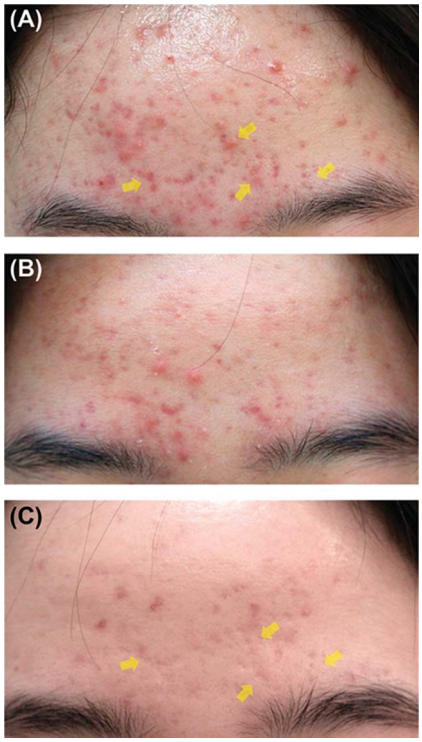

Figure 1. The natural course of inflammatory acne and acne scar development. (A) Baseline image of a 16-year-old female patient before systemic isotretinoin. (B) Six months after systemic isotretinoin (20 mg/kg/daily). (C) Eighteen months after systemic isotretinoin after achieving (≥150 mg/kg); yellow arrows indicate matching atrophic scars developed in inflammatory lesions on baseline photograph (A).

Among 71 patients, 43 had concomitant treatment with systemic isotretinoin (20 mg/daily, targeting 120–150 mg/kg) during the intervention or discontinued treatment within 3 weeks (Table 3) (Figure 3). The SGA score was compared between patients receiving systemic isotretinoin (n = 43) and the non-treated group (n = 28) after 3 sessions of FMRF and AFL combination treatment. The decrease in scar severity was higher in the group using isotretinoin (3.19 ± 0.70–1.53 ± 0.53 vs 2.89 ± 0.74–1.46 ± 0.51; $p < .05$, Mann–Whitney U test). In addition, the Global Improvement Score for skin texture was compared between the 2 groups (Figure 4). Concomitant isotretinoin yielded a higher improvement in skin texture after 3 sessions of FMRF and AFL (3.23 ± 0.70 vs 2.91 ± 0.69; Table 4).

Safety

The procedure was tolerable, and no patients required sedation other than topical anesthesia. Notably, 43 patients recently discontinued systemic retinoids (within 1 month) or concomitantly received systemic retinoids during the treatment course. No patient reported delayed wound healing or adverse events after the procedure. Among 3 patients who developed clinical signs of acral dermatitis related to systemic retinoid acid, there were no delays in wound healing of the laser-treated lesions. Patients reported transient erythema and edema immediately after treatment, and these resolved within hours to 7 days after treatment.

Discussion

Acne scars and inflammatory acne have substantial social implications, especially in young adults. Current systemic or topical options are ineffective treatments for atrophic acne scars. Thus, acne scar treatment is primarily nonpharmacologic.[16] Inflammatory lesions and atrophic acne scars often present simultaneously.[2,16] Severity of inflammatory lesions, family history, duration longer than a year, and squeezing or picking of acne lesions represent significant risk factors for scar-prone patients.[16,17] Therefore, early intervention

TABLE 4. Overall Treatment Outcome

Group	*Systemic Isotretinoin*	*FMRF and AFL*	*Total*
No. of patients, *n* (%)	43 (60.56)	28 (39.44)	71 (100)
Scar Global Assessment (SGA)			
Baseline	3.19 ± 0.70	2.89 ± 0.74	3.14 ± 0.76
Post 3 sessions	1.53 ± 0.63*	1.46 ± 0.51	1.58 ± 0.70
Global improvement score (GIS)	3.23 ± 0.70	2.91 ± 0.69	3.11 ± 0.71

*$p < .05$, Mann–Whitney *U* test.
AFL, ablative fractional laser; FMRF, fractional microneedle radiofrequency.

with selective multimodal approaches can markedly improve quality of life.

Microneedling devices were historically used as scar treatments to improve skin texture by inducing microscopic epidermal perforations.[18] However, traditional needling devices are associated with significant scarring in patients with dark skin.[19] When coupled with RF, alternating high-frequency electrical currents bypass the epidermis and promote dermal neocollagenesis and elastogenesis.[7] Previous reports on the animal model have shown that RF induces selective destruction of sebaceous glands and decreased sebum production.[20] Histologic analysis on patients who had RF-treated acne scars demonstrates coagulation and fragmentation of sebaceous glands.[7] Therefore, RF may benefit inflammatory acne lesions with sustained reduction of sebaceous hyperplasia.[21] Successful treatment outcomes have been reported in several studies. Fractional microneedle RF can be applied for both inflammatory lesions and atrophic acne scars with a favorable safety profile.[7–10,21] By contrast, AFL induces arrays of MTZs with controlled depth and no injury to surrounding tissue.[22,23] Expression of heat shock proteins, transforming growth factor beta, and matrix metalloproteinase-9

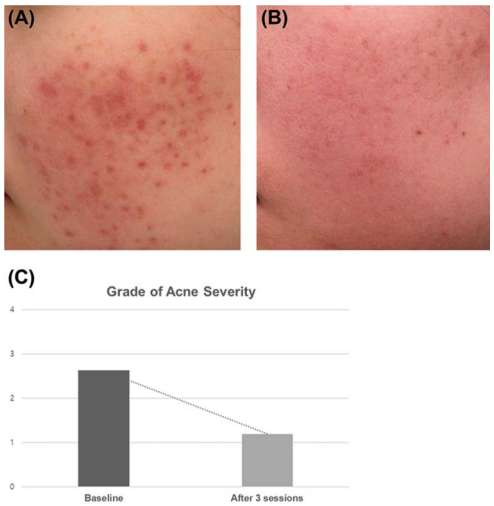

Figure 2. Clinical photographs of patients with inflammatory acne. (A) Baseline image of a 19-year-old female patient. (B) Four months after 3 sessions of combination FMRF and AFL treatment while continuing systemic isotretinoin (20 mg/kg/daily). (C) In the inflammatory acne group, all patients were treated with systemic isotretinoin during combination FMRF and AFL treatment. The grade of acne severity was significantly reduced after 3 sessions. ($n = 30$, *$p < .05$, Wilcoxon signed-rank test). AFL, ablative fractional laser; FMRF, fractional microneedle radiofrequency.

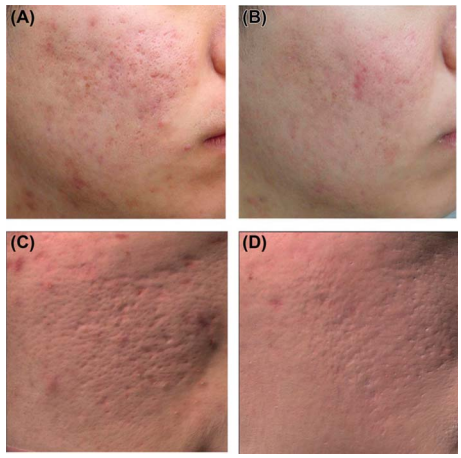

Figure 3. Clinical photographs of patients with concomitant isotretinoin use. (A) Baseline image of a 24-year-old male patient. (B) Four months after 3 sessions of combination FMRF and AFL treatment while continuing systemic isotretinoin (20 mg/kg/daily). (C) Baseline image of a 29-year-old male patient who discontinued isotretinoin at the onset of combination FMRF and AFL treatment. The images were taken on a 3D imaging system (Antera 3D; Miravex, Dublin, Ireland). (D) Three months after 3 sessions of combination treatment. AFL, ablative fractional laser; FMRF, fractional microneedle radiofrequency.

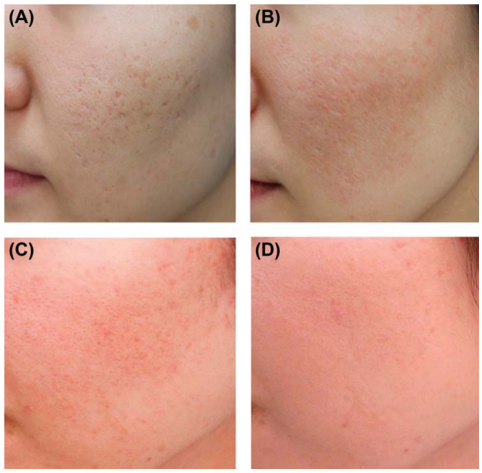

Figure 4. Clinical photographs of patients in acne scar group without systemic isotretinoin use. (A) Baseline image of a 32-year-old female patient presenting with mixed atrophic scar types. (B) Four months after 3 sessions of combination FMRF and AFL treatment. (C) Baseline image of a 26-year-old female patient who discontinued isotretinoin at the onset of combination FMRF and AFL treatment. (D) Four months after 3 sessions of combination treatment. AFL, ablative fractional laser; FMRF, fractional microneedle radiofrequency.

(MMP-9), which are crucial mediators of extracellular matrix remodeling, increase after AFL.[24,25] Heat shock proteins induced by AFL systems act as early responders to promote anti-inflammatory effects and long-term effectors promoting neocollagenesis.[5]

In the authors' study, each patient received combination treatment with FMRF immediately followed by AFL on the FMRF-treated area. The authors expect that the microneedle RF system creates an initial mechanical disruption of dermal fibrotic strands, tethering the atrophic acne scar and simultaneously delivering an optimal electromagnetic field to induce collagen remodeling.[8] Afterward, AFL irradiation achieves controlled tissue vaporization in the demarcated margins of acne scars, further refining the epidermal texture. Therefore, the combination treatment exerts a synergistic effect by inducing photothermal damage to sebaceous glands of inflammatory lesions and textural improvement to acne scars.

Treatment-related pain, immediate erythema, and edema were unavoidable in all patients. Post-inflammatory hyperpigmentation is one of the most concerning adverse effects of ablative resurfacing in patients with darker skin, with a reported overall incidence of 11.1% to 17.1% in the Asian population.[4,26] However, the authors did not observe any persistent side effects, including prolonged inflammatory reactions or scarring, related to the combination of FMRF and AFL.[19] Furthermore, although most patients included in the study were on low-dose systemic isotretinoin,[27] the authors did not observe delayed wound healing or hypertrophic scarring.

Systemic isotretinoin is the only therapeutic option that acts on all stages of acne pathogenesis but is commonly perceived to cause abnormal wound healing.[28] Early reports recommend postponing surgical procedures if a patient is taking retinoid or has discontinued retinoid use within the last 6 to 12 months.[29] However, to achieve optimal treatment outcomes in acne scar-prone individuals,[3,17] there is significant overlap between isotretinoin intake and nonpharmacological interventions depending on the clinical settings. During the past decade, numerous systematic reviews demonstrate a lack of atypical scarring by ablative and non-AFLs.[28] In the authors' study, they treated patients with low systemic isotretinoin, and because of the short study period, the effect of isotretinoin alone would not have led to significant clinical improvement in acne severity. the authors' results are consistent with recent reports demonstrating that invasive laser treatment and other procedures during isotretinoin treatment are relatively safe and do not increase the risk of poor wound healing or alter underlying wound healing potential.[12,13,16,28]

To the best of the authors' knowledge, this is the largest study to date to examine the use of FMRF in acne patients. Moreover, this is the first study to evaluate the efficacy of FMRF and AFL combination treatment, as well as the use of FMRF with concomitant isotretinoin intake. From this study, the authors have demonstrated the safety of concomitant isotretinoin intake while undergoing ablative lasers and EBD treatment. A potential limitation of the study is the retrospective nature without a control group. Also, despite the use of low dosage, a

significant quota of the study group was on systemic isotretinoin, which makes it difficult to conclude that the efficacy of the combination therapy is superior to previously reported approaches. Therefore, a prospective, split-face study with histological examination to objectively assess molecular changes after RF and laser irradiation is required. Additional studies are also needed to evaluate the underlying molecular mechanisms associated with use of systemic isotretinoin and FMRF.

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