A Prospective, Split-Face, Comparative Study of Combined Treatment With Fractional Microneedle Radiofrequency and Nonablative 1927-nm Fractional Thulium Fiber Laser for Wrinkle Treatment

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BACKGROUND Fractional microneedle radiofrequency (FMR) and nonablative 1927-nm fractional thulium fiber laser (TFL) are widely used for skin rejuvenation treatment.

OBJECTIVES To investigate the efficacy and safety of combined treatment with both devices for wrinkles.

PATIENTS AND METHODS Twenty-five patients with wrinkles were enrolled. One side of the face was treated with FMR alone, while the other side was treated with a combination of FMR and TFL. Each treatment consisted of 3 sessions at four-week intervals and patients were followed up 12 weeks after the last treatment. Overall improvement was assessed by patient global assessment (PGA) and investigator global assessment (IGA). Depression scores for the evaluation of wrinkles were objectively assessed by Antera 3D system.

RESULTS Both sides of the face led to clinical improvement in both mean PGA and IGA. Combination treatment demonstrated a greater improvement in both mean PGA and IGA compared with FMR alone. In addition, wrinkle grading scales and depression scores showed greater improvement in the combination group than in FMR alone.

CONCLUSION This study demonstrated that FMR and TFL comprise a good combination treatment for the treatment of wrinkles because both treatments have a synergistic effect on wrinkle improvement.

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Skin aging, which is a complicated biological process that occurs through intrinsic and extrinsic processes, is characterized by wrinkling, telangiectasia, dyschromia, laxity, and rough texture. Intrinsic aging is the natural aging process that results from slow irreversible tissue degeneration, including thinning of the epidermis and changes in collagen and elastic fibers. Extrinsic aging is often influenced by sun exposure, which causes brown spots and roughness in the epidermis and a decrease in the quantity and quality of collagen and elastin fibers in the dermis, which lead to skin laxity and to an increase in fine and deep wrinkles. Because skin aging has become a major cosmetic concern, various laser devices have been developed for skin rejuvenation. Recently, to meet the demand for aesthetic improvement with minimal risk and rapid recovery, a wide range of nonablative interventions are now being preferred by physicians and patients alike.[1]

Fractional microneedle radiofrequency (FMR) is a minimally invasive treatment that combines radiofrequency (RF) and microneedles and delivers RF current through a microneedle electrode assembly. The delivered RF into the skin promotes tissue regeneration by neocollagenesis and neoelastogenesis and is

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therefore frequently used in dermatology to treat skin laxity, rhytides, and scarring.[2,3] Nonablative 1927-nm fractional thulium fiber laser (TFL) treatment has demonstrated its effectiveness in pigment disorders including melasma, lentigines, and postinflammatory hyperpigmentation (PIH), and other superficial lesions such as seborrheic keratosis and actinic keratosis. Furthermore, several studies have shown that TFL improves photoaging, wrinkling, skin laxity, and texture, resulting from dermal effects of the laser. Thulium fiber laser treatment results in a high absorption of water, conferring greater ability to target superficial layers of the skin such as the epidermis and papillary dermis; therefore, it can improve not only epidermal pathologies including pigmentation but also dermal conditions via collagen neogenesis.[4] Consequently, both FMR and TFL have been independently used for skin rejuvenation treatment.

In this study, we conducted a prospective, split-face, comparative study to propose a good combination treatment with superior efficacy using both FMR and TFL for the treatment of wrinkles by building on the strengths of both treatments.

Materials and Methods

Study Design and Subjects

The study was conducted based on a prospective, split-face, comparative study that compared clinical efficacy between 2 facial sides either receiving combined treatment of FMR and TFL or FMR alone for facial wrinkles. This prospective study was approved by the Institutional Review Board and Ethics Committee of Severance Hospital. In total, 25 healthy subjects (2 men and 23 women, aged 45–62 years) with varying degrees of wrinkles were enrolled. Written informed consent was obtained from all subjects before enrollment. Subjects were excluded if they had acute or chronic illness, including concomitant skin disorders, pregnancy, lactation, or hemophilic condition. None of the patients underwent other skin treatments, including chemical, mechanical, or laser resurfacing, during the study period. We also excluded patients who had received any treatment affecting wrinkles for 3 months before the start of this study.

Devices and Treatment Protocols

Before treatment, the entire face was completely cleansed with a skin cleanser followed by the application of a topical EMLA cream (AstraZeneca AB, Södertälje, Sweden) for 30 minutes. The left half of the face was treated using the FMR device (GENIUSTM; Lutronic Corp., Goyang, Korea) followed by 1,927-nm TFL (LASEMDTM; Lutronic Corp.) and the right side of the face was treated using the FMR device only. Treatment was performed on 3 consecutive sessions at 4-week intervals and the last follow-up visit was 12 weeks after the final third treatment. FMR setting parameters of 1.0- to 1.9-mm needle depth, 20 to 50 mJ/pin and 2 to 3 passes were used and these parameters were changed depending on the part of the face and for each pass. The parameters for the TFL system included power at 5W, pulse energy at 15 to 20 mJ, the advanced and random-mode, and 4 passes on the full face, except for the periorbital areas and nose, which were treated with 8 passes. After treatment, the area was cooled with ice packs for 20 minutes and a mask pack was applied. All subjects were advised to avoid sun exposure and wear broad-spectrum sunscreen during and after the treatment period.

Assessment of Clinical Effects

On each visit, patient-subjective assessments were performed, and standardized digital photographs were taken under the same camera settings. Images were acquired using an Antera 3D camera, which is a novel device for image acquisition and analysis of skin conditions such as wrinkles, texture, pores, depressions, elevation, melanin, and hemoglobin. Patient global assessment (PGA) was evaluated according to patient satisfaction on a 4-point scale (0, unsatisfied; 1, slightly satisfied; 2, satisfied; and 3, very satisfied) especially for wrinkles and laxity at 12 weeks after the final treatment compared with pretreatment. The photographs before and after treatment were evaluated at the end of the study by 5 independent board-certified dermatologists who were not informed about which side was treated with combination treatment. Accordingly, investigator global assessment (IGA) was evaluated using a 5-point wrinkle grading scale[5] on each anatomical landmark (forehead, crow's feet,

nasolabial fold [NLF], marionette line, and neck wrinkles) together with the degree of improvement (Grade 0, no improvement; 1, 1–25% improvement; 2, 25–50% improvement; 3, 50–75% improvement; and 4, 75–100% improvement). Regarding 3D images, we focused on depression scores on the forehead, crow's feet, and NLF, which represent the affected area of the region of interest below the zero-reference surface, indicating skin wrinkles.

Assessment of Histologic Changes

Skin biopsies were performed on 6 volunteers. The specimens were obtained from all 6 volunteers before treatment, and 1 week after first treatment, skin specimens from both treated sides of the chins were obtained from a half of volunteers ($n = 3$) and 12 weeks after final treatment, skin specimens were obtained from another 3 people using a 2-mm punch. Skin tissues were stained with hematoxylin and eosin (H&E), Masson trichrome, and Verhoeff–Van Gieson. Images of each stain section were taken using a 12.5-megapixel digital camera (DP70; Olympus Optical Co., Tokyo, Japan) connected to a light microscope (BX40; Olympus Optical Co.).

Statistical Analysis

The paired *t*-test was used to compare differences in PGA, IGA, and depression scores before and after treatment or between combined treatment and FMR alone (SPSS version 19.0, SPSS Inc., Chicago, IL). The χ-square test was also performed for comparison between combined treatment and FMR alone. All *p*-values were 2 tailed, and differences were considered significant when $p < .05$.

Results

All had Fitzpatrick skin Type III or IV with mild-to-severe facial wrinkles. Both FMR alone and combination treatment with TFL led to subjective improvement, and the combination treatment demonstrated greater patient satisfaction compared with FMR treatment alone (mean PGA 2.28 ± 0.68 vs 1.48 ± 0.77, $p < .001$). In the combination treatment, 10 patients (40%) were very satisfied, 12 patients (48%) were satisfied, and 3 patients (12%) were slightly satisfied. In FMR treatment alone, 2 patients (8%) were very satisfied, 10 patients (40%) were satisfied, 11 patients (44%) were slightly satisfied, and 2 patients (8%) were unsatisfied. The ratio of patients who exceeded PGA scores of 2.0 was significantly higher in the combination treatment relative to FMR treatment alone (88% vs 48%, $p < .01$).

Mean IGA scores evaluated by independent dermatologists using clinical photographs before and after treatment were higher in the combination treatment relative to FMR alone (1.95 ± 0.47 and 1.54 ± 0.39, respectively, $p < .001$) and the ratio of patients who exceeded IGA scores of 2.0 was significantly higher in the combination treatment than FMR treatment alone (60% vs 8%, $p < .001$). In addition, wrinkle grading scales of IGA on the forehead, crow's feet, NLF, marionette lines, and neck line were significantly decreased in both treatment groups and the combination treatment showed a greater decrease in wrinkle grading scale 3 months after the last treatment relative to FMR treatment alone ($p < .001$). The most significant change in wrinkle grading scale between the before and after treatment were noted in the forehead (Figure 1A,B), crow's feet (Figure 1C,F), and neck lines, followed by NLF and marionette lines.

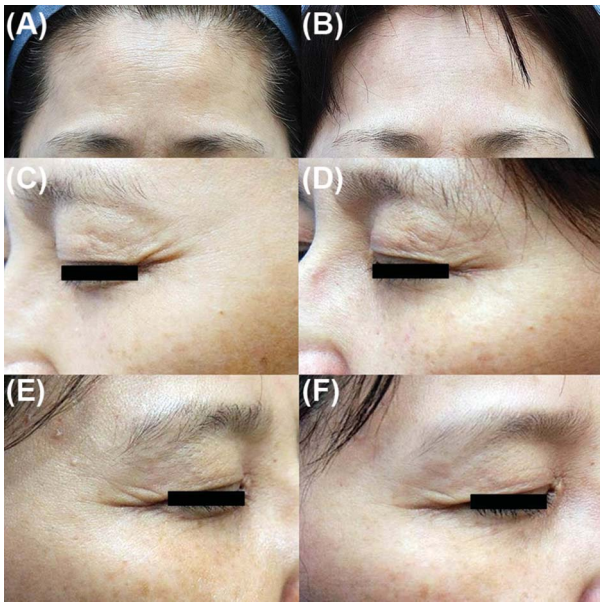

Figure 1. A patient who showed significant improvement in the forehead (A), crow's feet (C and E) at baseline and at 12 weeks after final treatment (B, D, F). Left side FMR + TFL, right side only FMR.

Antera 3D photographs showed that both treatment groups led to significant clinical improvement and the change in roughness, depression, and elevation on the forehead, crow's feet, and NLF were significantly improved in both combination treatment and FMR treatment alone. In particular, an improvement in depression parameter reflecting wrinkle severity in the forehead, crow's feet, and NLF was significantly observed in the combination treatment relative to FMR treatment alone ($p < .05$, baseline vs 12-week after final treatment). Wrinkle depression in the forehead (Figure 2) was evaluated with the Antera 3D system at baseline (V1) and at 12 weeks after final treatment (V5).

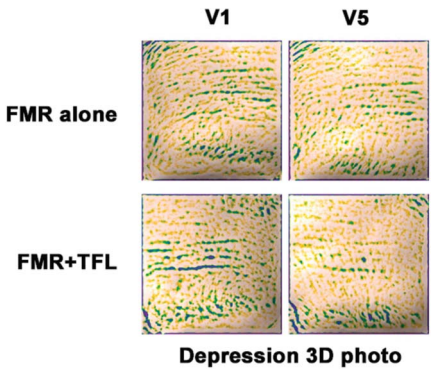

Figure 2. Improvement of depression scores in the forehead assessed with the 3D system at baseline (V1) and at 12-weeks after final treatment (V5).

The histologic findings of 1 week after the first treatment showed that FMR induced coagulated columns with mixed cellular infiltration, neovascularization, and neocollagenesis in mid-to-deep dermis (Figure 3A). In addition, TFL induced both coagulation necrosis of epidermis and well-defined dermo-epidermal clefts, denatured areas of the upper dermis (Figure 3B). Both treatment regimens demonstrated increased collagen (Figure 3C–E) and elastic fibers 3 months after the final treatment compared with baseline.

Almost all patients experienced mild pain during laser treatment. Swelling and edema, which were observed after the treatment, were resolved within 1 to 3 days. Two patients developed mild dermatitis after the procedure but no sequelae were seen. Other adverse events, such as thermal injury, bullae, post-therapy scarring or PIH, and secondary infection were not observed.

Discussion

In recent years, there has been a growth in demand for aesthetic nonsurgical procedures to improve skin imperfections.[6] Traditional skin rejuvenation methods such as surgery and ablative laser treatment can dramatically improve skin tone and texture, but they require long recovery periods and have an increased risk of complications.[1] Accordingly, noninvasive and minimally invasive aesthetic approaches have already become an important aspect in antiaging treatment.

Fractional microneedle RF and TFL, which were used in this study to evaluate the efficacy of their combined treatment in the treatment of wrinkles, have been widely used as one of the major nonoperative skin rejuvenating treatments.[1] Heating the dermal layer using RF devices stimulates the formation of new collagen and elastin fibers, resulting in the improvement of wrinkles and laxity along with skin tightening and a lifting effect.[6] Radiofrequency treatments have reportedly induced an active dermal remodeling process due to the increased expression of heat shock proteins, metalloproteinases, and inflammatory cytokines.[7] Fractionated RF with microneedles, FMR, took a large step toward offering laser-like efficacy with much less downtime, high tolerability, and an excellent safety

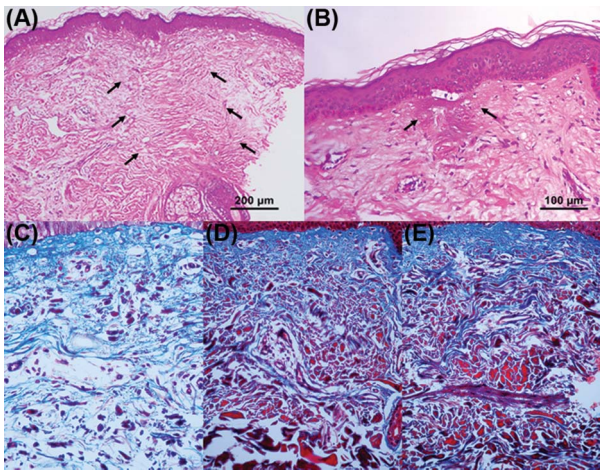

Figure 3. Hematoxylin and eosin (H&E) stain of FMR-induced collagen remodelling in the mid–deep dermis (A) and TFL-induced coagulation on dermal–epidermal junction (B) 1 week after treatment. Before treatment (C) and 3 months after FMR alone (D) and FMR with TFL combination treatment (E). Masson trichrome staining (C–E).

profile relative to fractional ablative lasers.[1,8] Microneedling in FMR brings therapeutic effects on the epidermis inducing textural improvement, even though FMR does not leave direct heat damage to the epidermis.[9] Therefore, FMR may promote collagen remodeling and skin contraction without excessive epidermal damage, serving as a means to improve the appearance of photodamaged skin. The RF emission time and the depth of needle insertion can be easily changed at the operator's discretion to specifically target either the superficial or deep dermis for various dermatologic conditions.[6] Recently, Lu and colleagues[10] compared the effect of FMR on skin laxity through different target approaches into deep and superficial dermal layers in the same patient. They noted that the deep dermal approach was significantly better for the treatment of skin laxity relative to the superficial approach, suggesting that the deep dermal FMR approach would be more suitable for wrinkle treatment.

Fractional photothermolysis (FP) is a technique in which an array of microscopic thermal wounds is induced in the skin to stimulate a therapeutic response in the dermis. Thulium fiber laser, which was used in this study, is an FP system that is, applied using a novel 1,927-nm wavelength. Because TFL is characterized by high-water absorption that can target the epidermal layer and the superficial dermal layer, it can improve not only epidermal lesions, including pigmentation but also dermal conditions such as wrinkles.[11,12] Geronemus[13] reported improvement in fine-to-moderate rhytides with TFL, with less improvement for deeper wrinkle lines. Lee and colleagues[14] demonstrated melanin reduction and procollagen type-3 induction, supporting the efficacy of TFL for the treatment of photoaged skin. In addition, TFL has been suggested for use as a fractional laser system as an effective and safe treatment, especially on darker Fitzpatrick skin types.[15]

Likewise, each device has its own advantages relative to physical properties in tissue interaction. We therefore wanted to investigate a suitable combination treatment as a more-effective and safer choice for skin rejuvenation to maximize the effect on skin rejuvenation. Among the various possible combinations, a combination of FMR and TFL was decided on for this study because FMR can target the middle and deep dermis using a suitable needle depth and TFL can focus on the epidermis and papillary dermis because of its high water absorption property. As a result, this study indicates that both FMR alone and in combination with TFL led to significant clinical improvement in wrinkles. In addition, FMR and TFL combination treatment showed greater efficacy without increased risk of side effects for the treatment of wrinkles in Asian patients based on both patient satisfaction and objective evaluations. Most patients expressed their satisfaction in skin tightening and lifting in the combination treatment relative to FMR treatment alone. Objective assessment using wrinkle grading scales demonstrated that the forehead, neckline, and crow's feet showed relatively large improvement after treatment. As with the forehead, the periorbital area and the neck are the thinnest parts of the skin; thus, wrinkles in these anatomic areas seem to show the best response to treatment relative to other skin areas.[16,17]

Using images from the Antera 3D camera, we assessed changes in roughness, depression, and elevation of the forehead, crow's feet, and NLF. Both FMR alone and in combination with TFL led to significant improvement in wrinkles. Of the parameters, the improvement of depression in all anatomical landmarks was significantly observed in combination treatment relative to FMR treatment alone. In the evaluation through 3D camera images, the greatest improvement in wrinkles was noted in the forehead and significant improvement was also observed in crow's feet and NLF after treatment, in particular with combination treatment. As the analysis of depression through 3D camera images was correlated with IGA using the wrinkle grading scale, our study suggests that depression scores in 3D camera images can be effectively used for the evaluation of wrinkles.

A pronounced and consistent histologic change of aged skin is the flattening of the dermal–epidermal junction and a loss of rete ridges in the epidermis and a reduction of collagen Types I and III. Solar elastosis, which is the striking histologic change of photodamaged dermis, occurs in the replacement of elastic fibers with altered elastotic material and is located near the dermal–epidermal junction.[18,19] Therefore, we believed that the epidermis and papillary dermis, where changes in skin aging are more apparent rather

than in the mid-dermis and deep dermis, are surely to be included as the extent of skin layers to be treated for wrinkles. However, as it is known that the effect of FMR on skin laxity is better when the target is to the deep dermal layer rather than the superficial layer,[9] this approach can spare the epidermis and papillary dermis even if microneedling can have some effect on these layers. However, mechanical microneedling may not be enough to stimulate tissue regeneration especially in case of insulated microneedles. Therefore, we designed the combination treatment of TFL along with FMR to propose a powerful combination for the treatment of wrinkles, because TFL delivers highly controlled subablative damage to the epidermis with very superficial coagulation in the superficial dermis.

In our study, we confirmed that the combined treatment of FMR and TFL is a good treatment combination for skin rejuvenation showing synergistic effects through targeting different levels of skin layers. Even if the combination treatment in the same session has the potential risk of bulk heating, no serious adverse events occurred in the present study because the 2 devices target different levels of the skin. To reduce any risk of heat damage, we applied an ice bag after each pass. When both FMR and TFL are treated at the same time, the order of treatment was FMR followed by TFL because the order of treatment has an advantage to stop pinpoint bleeding by FMR via epidermal coagulation by subablative damage to the epidermis. In addition, lower treatment densities should enhance the safety of their combination.

A preliminary study in which FMR and TFL were applied at the same time for skin rejuvenation was performed.[8] The pilot study suggested that the combination treatment was safe and effective, and produced synergistic results without serious adverse events in skin rejuvenation. However, the previous study had several limitations, including few patients, no control group, and no objective assessment. Therefore, to prove the efficacy and safety of the combination treatment for wrinkles, we performed a prospective, split-face controlled study with a large number of patients to compare the combination FMR and TFL treatment and FMR alone using an objective assessment, including 3D camera images and histological evaluation. Nevertheless, there are still some limitations to this study. We enrolled subjects with various grades based on the wrinkle grading scale. This study was conducted in Asians only, so the results cannot be generalized to other populations with different Fitzpatrick skin phototypes.

We propose that combination treatment using FMR and TFL may be a promising combination for the treatment of wrinkles. More extensive follow-up is needed to confirm the safety and the maintenance of effectiveness and further studies are required to evaluate the most effective laser parameters for skin rejuvenation.

References

1. Zhang M, Fang J, Wu Q, Lin T. A prospective study of the safety and efficacy of a microneedle fractional radiofrequency system for global facial photoaging in Chinese patients. Dermatol Surg 2018;44: 964–70.
2. Seo KY, Yoon MS, Kim DH, Lee HJ. Skin rejuvenation by microneedle fractional radiofrequency treatment in Asian skin; clinicaland histological analysis. Lasers Surg Med 2012;44:631–6.
3. Weiss RA. Noninvasive radio frequency for skin tightening and body contouring. Semin Cutan Med Surg 2013;32:9–17.
4. Kwon IH, Bae Y, Yeo UC, Lee JY, et al. Histologic analyses on the response of the skin to 1,927-nm fractional thulium fiber laser treatment. J Cosmet Lser Ther 2018;20:12–6.
5. Carruthers A, Carruthers J. A validated facial grading scale: the future of facial ageing measurement tools? J Cosmet Laser Ther 2010;12: 235–41.
6. Kaplan H, Kaplan L. Combination of microneedle radiofrequency (RF), fractional RF skin resurfacing and multi-source non-ablative skin tightening for minimal-downtime, full-face skin rejuvenation. J Cosmet Laser Ther 2016; 18:438–41.
7. Zheng Z, Goo B, Kim DY, Kang JS, et al. Histometric analysis of skin-radiofrequency interaction using a fractionated microneedle delivery system. Dermatol Surg 2014;40:134–41.
8. Chun S. Fractional microneedling radiofrequency and fractional 1927 nm thulium laser treatment offer synergistic skin rejuvenation: a pilot case series. Laser Ther 2018;27:283–91.
9. Park HJ, Kim HM, Oh MJ. Clinical study of facial wrinkle treatment with fractional microneedle radio frequency system. Med Laser 2014;3:59–64.
10. Lu W, Wu P, Zhang Z, Chen J, et al. Curative effects of microneedle fractional radiofrequency system on skin laxity in Asian patients: a prospective, double-blind, randomized, controlled face-split study. J Cosmet Laser Ther 2017;19:83–8.
11. Polder KD, Harrison A, Eubanks LE, Bruce S. 1,927-nm fractional thulium fiber laser for the treatment of nonfacial photodamage: a pilot study. Dermatol Surg 2011;37:342–8.

12. Boen M, Wilson MJV, Goldman MP, Wu DC. Rejuvenation of the male scalp using 1,927nmNon-ablative fractional thulium fiber laser. Lasers Surg Med 2017;49:475–9.

13. Geronemus RG. Fractional photothermolysis: current and future applications. Lasers Surg Med 2006;38:169–76.

14. Lee HM, Haw S, Kim JK, Chang SE, et al. A split-face study using the 1,927-nm thulium fiber fractional laser for photoaging and melasma in asian skin. Dermatol Surg 2013;39:879–88.

15. Polder KD. Commentary: a split-face study using the 1,927-nm thulium fiber fractional laser for photoaging and melasma in asian skin. Dermatol Surg 2013;39:889–90.

16. Ha RY, Nojima K, Adams WP Jr, Brown SA. Analysis of facial skin thickness: defining the relative thickness index. Plast Reconstr Surg 2005;115:1769–73.

17. Chopra K, Calva D, Sosin M, Tadisina KK, et al. A comprehensive examination of topographic thickness of skin in the human face. Aesthet Surg 2015;35:1007–13.

18. Tobin DJ. Introduction to skin aging. J Tissue Viability 2017;26: 37–46.

19. Yaar M, Gilchrest BA. Photoageing: mechanism, prevention and therapy. Br J Dermatol 2007;157:874–87.

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