Comparison of Microneedle Fractional Radiofrequency Therapy with Intradermal Botulinum Toxin A Injection for Periorbital Rejuvenation

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Key Words
Botulinum toxin A · Microneedle fractional radiofrequency · Periorbital wrinkles · Rejuvenation

Abstract
Background: For periorbital rejuvenation, injection of botulinum toxin A (BoNT/A) is known to improve both static as well as dynamic wrinkles. A microneedle fractional radiofrequency (MFR) device was recently developed and is a novel and promising tool. Objective: This study compares the effects of these two treatment modalities on periorbital static wrinkles and lines. Methods: Twelve healthy women aged 20–59 years with periorbital wrinkles participated in this study. Each patient received one session of intradermal injection of BoNT/A on the left periorbital area and three sessions of MFR on the right. Clinical improvement, skin elasticity and subjective satisfaction were evaluated at every visit (baseline, 3, 6 and 18 weeks). Results: BoNT/A injection showed superior effects at 3 and 6 weeks. However, the MFR device showed better improvement at 18 weeks. In skin biopsies, the expression of procollagen 3 and elastin was increased on the MFR side compared to the untreated skin and the BoNT/A injection side. The patient satisfaction surveys at 3 weeks showed better satisfaction on the BoNT/A treatment side compared to the MFR treatment side. At 18 weeks, there were no significant differences in patient satisfaction between the two sides. Conclusion: BoNT/A injection rapidly improved periorbital wrinkles, but the effect decreased up to week 18. Compared to BoNT/A injection, MFR therapy showed gradual and long-term improvement in periorbital rejuvenation.

Introduction
Periorbital wrinkles are the result of muscle contraction and photoaging [1]. Static wrinkles and lines in a resting position result from long-term, repeated contraction of the orbicularis oris muscles and UV-induced dermal collagen degeneration.

Several therapeutic modalities have been utilized for periorbital rejuvenation, including surgery, chemical peeling, botulinum toxin or filler injection and various laser devices [2–9]. Multiple intradermal injections of botulinum toxin A (BoNT/A) are known to improve both
static wrinkles and lines as well as dynamic wrinkles [1]. Recently, a microneedle fractional radiofrequency (MFR) device was developed, a novel and promising tool for facial rejuvenation [4]. The aim of this prospective, split-face, comparative pilot study was to evaluate and compare the effects of these two treatment modalities on periorbital static wrinkles and lines.

**Patients and Methods**

**Patients**

Twelve healthy Korean women aged 20–59 years with periorbital wrinkles with scores of 3–5 on the baseline facial fine wrinkle grading scale [10] (table 1) were included in the study. Patients with a history of injection with collagen, fat or hyaluronic acid, of dermabrasion, phenol peel, ablative or lifting surgery, or of nonablative or ablative skin resurfacing laser treatment within 2 years prior were excluded. Patients with infectious or inflammatory skin disease, keloid formation or chronic disease were also excluded. All patients were informed of the aim, process, benefits and possible complications of the study, and written consent was obtained before treatment. This study was approved by the institutional review board of Gangnam Severance Hospital (3-2011-0244).

**Treatment Protocols**

Each patient received one session of BoNT/A injection on the left periorbital area and three sessions of MFR therapy on the right periorbital area. BoNT/A (MEDITOXIN®, Medytox Inc., Seoul, Korea) injections were administered at baseline, using 1-ml syringes attached to 30-gauge needles. One vial (50 units) of BoNT/A was reconstituted with 0.9% sterile saline to give 1 unit of BoNT/A per 0.1-ml injection. A total of 5 units were divided and superficially injected into 6–9 treatment sites, which were spaced approximately 0.5 cm apart from each other, on the lateral aspects of the orbicularis oculi muscles, from 1.5 cm lateral to the orbital rim. MFR therapy (INFINI®, Lutronic, Seoul, Korea) was performed for three sessions: at baseline, 3 and 6 weeks. This device delivers bipolar radiofrequency energy into the dermis through 49 micro-electrodes. Each needle is insulated with gold and silicon except at the end of the tip, which generates radiofrequency energy without thermal damage to the epidermis. The device can generate a maximum power of 500 W, and the energy can be controlled at levels from 1 to 20. Before every procedure, 5% EMLA cream (Eutectic Mixture of Lidocaine and Prilocaine; Korea AstraZeneca, Seoul, Korea) was applied over the periorbital area. The treatment area was cleansed and completely dried. Each procedure was performed at a depth of 0.5 mm for 80 ms with a 150 W (level 6) intensity for two passes. The treatment area was kept dry during the treatment.

**Outcome Assessments**

At each visit (baseline, 3, 6 and 18 weeks), photographs of both sides of the periorbital areas were taken using identical settings. Wrinkle grade and skin elasticity were evaluated by two well-trained dermatologists who did not participate in the treatment and were not informed of the treatment modalities on each side. The degree of wrinkling was determined on a baseline facial fine wrinkle grading scale (table 1). For elasticity measurements, a Cutometer® MPA 580 (Courage + Khazaka electronic GmbH, Cologne, Germany) was used. The Cutometer was placed on each side of the periorbital area, 1.5 cm outward from the lateral canthus. A negative pressure of 200 mbar was applied to the skin with a 2 mm suction pore for 2 s, followed by a 2-s relaxation time. Using the Cutometer MPA 580 software, average values of three measurements were obtained. The R2 ratio (Ua/Uf), which indicates the overall elasticity of the area, was documented and analyzed. At the final follow-up, patients were asked to rate their overall satisfaction on each side and to report any side effects. The satisfaction scale was as follows: 1 = not satisfied, 2 = slightly satisfied, 3 = satisfied, 4 = very satisfied.

| Table 1. Baseline facial fine wrinkle grading scale |
|-----------------|-----------------|-----------------|
| Grade 0         | no evidence of line or wrinkle |
| Grade 1         | a few short barely perceptible wrinkles |
| Grade 2         | a few shallow wrinkles discreetly visible with no deep wrinkles in the corners |
| Grade 3         | shallow easily visible wrinkles with 1 or 2 shorter deeper wrinkles in the corners |
| Grade 4         | moderate number of fine wrinkles nearly covering the entire area, with wrinkles deeper and longer in the corners |
| Grade 5         | many deep lines with several coarse wrinkles extending into the cheek area |

The degree of wrinkling was determined on a baseline facial fine wrinkle grading scale.

| Table 2. Demographics of the nine patients who completed the study |
|-----------------|-----------------|-----------------|
| Clinical variables | Number of patients |
| Total cases      | 9               |
| Age, years       |                 |
| Mean ± SD        | 47±44.4         |
| Range            | 41–54           |
| Gender           |                 |
| Male             | 0 (0%)          |
| Female           | 9 (100%)        |
| Fitzpatrick skin type |       |
| III              | 2 (22%)         |
| IV               | 7 (78%)         |
| Initial wrinkle grade | Right side | Left side |
| Grade 1          | 0               | 0           |
| Grade 2          | 0               | 0           |
| Grade 3          | 5 (56%)         | 4 (45%)     |
| Grade 4          | 3 (33%)         | 3 (33%)     |
| Grade 5          | 1 (11%)         | 2 (22%)     |
In one patient, a skin biopsy was performed on the treatment areas and the untreated temporal area near the eye at the final follow-up at week 18. To evaluate dermal elasticity, immunohistochemical staining (procollagen 1 and 3, collagen 4 and elastin) was performed. Image analysis was performed using Image Pro Plus version 4.5 (Media Cybernetics Co., Silver Spring, Md., USA). The amount of positive staining was recorded as the ratio of the positive area to the measured dermal area (PA/DA). A skin specimen taken from the forehead was used as control.

Results are expressed as mean ± standard deviation. Statistical analysis was performed using the SPSS software (version 16, SPSS Inc., Chicago, Ill., USA) using Student’s t test. p values <0.05 were considered to be statistically significant.

**Results**

**Demographics**

Of the twelve subjects enrolled, nine completed the study. Seven patients had Fitzpatrick skin type III and two patients had type IV. The mean age was 47 ± 4.44 years with a range of 41–54 years (table 2). One subject dropped out due to pain during MFR treatment after the second session, and two patients did not complete the follow-up.

**Clinical Improvement**

The degree of periorbital wrinkling was compared between the right MFR treatment side and the left BoNT/A treatment side at every visit (fig. 1). At baseline, the wrinkling grade on the MFR side (3.00 ± 0.86) and the BoNT/A side (3.11 ± 0.93) showed no significant differences (p = 0.79). The BoNT/A injection side showed rapid improvement, with superior results at 3 weeks (1.33 ± 0.50) and 6 weeks (1.67 ± 0.71) compared to the MFR treatment side at 3 weeks (2.89 ± 0.78) and 6 weeks (2.33 ± 0.50) (p < 0.0001, p = 0.036). However, the MFR treatment side showed gradual improvement and better improvement at 18 weeks (1.56 ± 0.73) compared to the BoNT/A injection side (2.33 ± 0.71) (p = 0.035; fig. 2).

**Elasticity**

The overall elasticity was evaluated by Cutometer and immunohistochemistry. The Cutometer R2 ratio showed no significant differences throughout the study period (fig. 3). Immunohistochemistry revealed that the expression of procollagen 3 and elastin was increased at final follow-up on the MFR treatment side compared to the untreated skin and the BoNT/A treatment side (fig. 4). The expression of procollagen 1 and collagen 4 was not different among these groups.

**Patient Satisfaction**

The patient satisfaction surveys at 3 weeks showed better satisfaction on the BoNT/A treatment side (3.00 ± 0.13) compared to the MFR treatment side (1.33 ± 0.50) (p < 0.0001). At 18 weeks, the patient satisfaction grade on the BoNT/A side (2.56 ± 0.73) and the MFR side (2.44 ± 0.73) showed no significant differences (p = 0.75; fig. 5).
Adverse Events

Patients seem to be more tolerant to BoNT/A than MFR treatment, since one patient dropped out due to pain during MFR treatment. Other patients reported minimal or no pain during MFR treatment, and there was no patient who complained of discomfort during BoNT/A treatment. Post-procedure bleeding on the MFR side was easily controlled by mild compression, and bruising improved within 1 week after treatment without secondary complications. Two of the nine subjects (22.2%) reported postinflammatory hyperpigmentation (PIH) on the MFR-treated side that resolved spontaneously within 2 months. There were no incidents of infection, bleeding, crusting or postinflammatory hypopigmentation or depressions on the MFR treatment side. Likewise, there were no reports of edema, bruising, pain or ptosis on the BoNT/A treatment side.

Discussion

BoNT/A injection has been the gold standard for periorbital rejuvenation. The orbicularis oculi muscle is the primary target of BoNT/A injection for the treatment of periorbital wrinkles. However, in older patients, prominent static wrinkles due to photoaging are less responsive to botulinum toxin injection alone [11]. The clinical effect of botulinum toxin injection is rapid, appearing within 1–2 days. However, its effect gradually decreases at 3–4 months after injection, and thus repeated injections are needed [12]. Edema, bruising and pain can occur at the injection site, and adverse effects like ptosis, muscle weakness and headache have been reported [13]. Recently, an MFR device was developed, a novel and promising tool for facial rejuvenation [4]. Therefore, the aim of our study was to compare the effects of BoNT/A injection and MFR treatment on periorbital static wrinkles and lines.

In this study, all subjects achieved meaningful improvement in periorbital wrinkles with both treatments at final follow-up. On the BoNT/A injection side, the effect was prominent at 3 and 6 weeks. On the MFR treatment side, the effect was unremarkable at 3 weeks, but showed gradual improvement at 6 weeks and at final follow-up. Similarly, patient satisfaction on the BoNT/A treatment side was better than on the MFR treatment side at 3 weeks, which decreased as time passed by, and there were no significant differences in patient satisfaction between the two sides at 18 weeks. Although the period of maximal improvement was not the same, final patient satisfaction was not different between the two treatments.

Noninvasive radiofrequency devices deliver thermal energy into the dermis, inducing contraction and remodeling of collagen bundles without damaging the epidermis [14]. Moreover, improvement in skin tightening lasts more than 6 months [15]. The MFR device inserts a microneedle into the dermis and directly delivers ther-

![Fig. 2. Mean wrinkling grades of periorbital wrinkles on both sides. Grades were evaluated at baseline, 3, 6 and 18 weeks. BoNT/A injection showed rapid improvement, presenting superior effects at 3 and 6 weeks (p < 0.05). However, MFR treatment showed gradual and better improvement at 18 weeks (p < 0.05). * p < 0.05.](image1)

![Fig. 3. Overall elasticity of the periorbital area as evaluated by the Cutometer. There were no significant differences between the two sides at any visit. There were no significant differences in elasticity improvement before and after treatment.](image2)
mal energy. The diameter of each microneedle is tiny (200 μm) and the procedure is minimally invasive. Radiofrequency energy is generated at the tip of the needle only, thus collagen contraction and reorientation can be achieved more efficiently and epidermal damage can be avoided more effectively than with a noninvasive radiofrequency device.

Aust et al. [16] reported that microneedling can increase collagen and elastin deposition, thus improving wrinkles and scars. The dermal matrix of the skin is composed of type I and type III collagen, glycosaminoglycans and elastin fibers [17]. Expression of procollagen can reflect the synthesis of type I and III collagen; mature skin predominantly consists of type I collagen, while newly synthesized skin mostly consists of type III collagen [18]. In our study, the expression of procollagen 3 and elastin was increased at final follow-up on the MFR-treated side, but the BoNT/A injection side did not show neoolastogenesis or neocollagenesis. An increase in procollagen 3, not procollagen 1, might represent current synthesis of collagen on the MFR-treated side. Since type III collagen not only plays an important role in maintaining the skin, but also gives elastic properties to the skin due to its disulfide bonds [19], an increase in procollagen 3 and elastin could support the beneficial effect of MFR on dermal elasticity. However, skin elasticity as measured by the Cutometer showed no significant difference between sides before and after treatment, since this instrument measures too superficially to detect dermal changes [20]. Our results suggest that MFR treatment can better regenerate collagen and elastic fibers compared to botulinum toxin and thus be effective for the rejuvenation of static wrinkles. The underlying
mechanism regarding regeneration of collagen and elastic fibers needs further investigation.

Lee et al. [4] reported that PIH appeared in 40% (nonablative) and 92% (ablative) of patients who received fractional photothermolysis treatments. In our study, two patients (22.2%) reported PIH on the MFR treatment side which resolved spontaneously within 2 months. An uneven contour of the periorbital area may prevent close contact of the tip to the skin, and an unskilled technician could expose the tip of the needle on the epidermis, delivering radiofrequency energy, which may result in PIH.

The limitation of this study was that the treatment sides were not randomized. Although two wrinkle evaluators did not participate in the treatment and were not informed of the treatment modalities on each side, this could have induced biases. In addition, since the timings of the maximal effects of the two modalities are different, accurate comparison of patient satisfaction was not feasible. Although we compared the satisfaction grades at the optimum efficacy points of the two modalities, the fact that the patients were not blinded to the treatment still presents a limitation.

This study compared the effects of MFR and BoNT/A injection on periorbital wrinkles. BoNT/A injection improved periorbital wrinkles and patient satisfaction rapidly, but the effect decreased up to the 18-week follow-up. On the other hand, MFR improved wrinkles slowly but gradually, and the improvement remained with better patient satisfaction at 18 weeks. In conclusion, MFR is a safe, long-term modality effective for periorbital rejuvenation. Since the target mechanisms and maximum effect times of MFR and BoNT/A injections are different, we suggest that a combination of the two modalities could generate a significant synergistic effect.

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Disclosure Statement

The authors declare no conflicts of interest.

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