

Research Article

A Novel Regimen of Transdermal Botulinum Toxin Delivery Using Fractional Microneedling Radiofrequency for Treatment of Erythema in Rosacea

Jin Seo Park , So Yeon Lee , Jin Cheol Kim , Chun Wook Park , Hye One Kim ,
and Bo Young Chung 

Department of Dermatology, Kangnam Sacred Heart Hospital, Hallym University College of Medicine,
Seoul 07441, Republic of Korea

Correspondence should be addressed to Bo Young Chung; victoryby@naver.com

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Facial erythema is a representative symptom of rosacea patients that greatly impairs quality of life. Recently, the therapeutic effects of intradermal injection of botulinum toxin type-A on erythema have been investigated. Fractional microneedling radiofrequency has been reported to be effective in dermal remodeling and anti-inflammation. To obtain enhanced therapeutic effects with a less painful and easier approach, a treatment regimen using transdermal botulinum toxin delivery with fractional microneedling radiofrequency was developed. We aimed at investigating the efficacy and safety of transdermal botulinum toxin delivery with fractional microneedling radiofrequency in treating the erythema of rosacea. This was a retrospective review of 20 patients with facial erythema associated with rosacea. All patients underwent two sessions of treatment at 4-week intervals. Standardized photographs were taken, and the clinicians' erythema assessment (CEA), erythema index (EI) measured through a spectrophotometer, investigator's global assessment (IGA), and subjective satisfaction and side effects were evaluated at the baseline and 4, 8, and 12 weeks after the baseline. Compared to the baseline, CEA levels significantly decreased after 8 weeks ($P = 0.018$) and 12 weeks ($P = 0.005$). As an objective measure, EI was observed to decrease significantly at 4 weeks ($P = 0.04$) and 8 weeks after the baseline ($P = 0.005$) compared with the baseline. Ninety-five percent of patients were either very satisfied or satisfied with the treatment. None of the patients experienced remarkable side effects. A novel treatment regimen involving transdermal botulinum toxin delivery and fractional microneedling radiofrequency may be an effective and safe option for reducing the facial erythema of rosacea.

1. Introduction

Rosacea is a chronic inflammatory skin condition characterized by persistent central facial erythema. It is relatively common, with a prevalence of 1–22% [1]. As rosacea adversely affects appearance and induces disturbing symptoms such as flushing, it can have a detrimental influence on the psychosocial well-being of patients. Common treatment options include oral antibiotics, topical medications such as metronidazole, and light-based therapy such as laser or intense pulsed light [2]. However, the response to treatment is often incomplete, and relapses are common, underscoring the need for new and efficient treatment options.

In recent years, intradermal botulinum toxin A (BTA) has been studied as a treatment for facial erythema, and many studies have demonstrated favorable outcomes [3–9]. Fractional microneedling radiofrequency (FMR) is an emerging treatment device used across various dermatological areas. In addition, FMR therapy has been reported to alleviate erythema related to rosacea [10, 11] and post-inflammatory erythema in patients with acne [12].

In this study, we adopted FMR to improve drug delivery while showing its synergistic effect with BTA on erythema improvement. We aimed at investigating the therapeutic effect of alleviating resistant erythema related to rosacea and the safety of the transdermal delivery of BTA with FMR.

2. Materials and Methods

2.1. Patients. We performed a retrospective chart review with 20 patients treated at a single center between January 2021 and April 2022. The patients presented with central facial erythema related to rosacea. Furthermore, conventional treatment modalities for rosacea had previously failed in these patients. Patients had not been previously treated for rosacea for at least 6 months. Exclusion criteria to the study treatment were as follows: (1) patients <18 years of age; (2) infection of the target area; (3) known hypersensitivity to any of the ingredients of BTA or local anesthetic cream; (4) pregnancy or lactation; and (5) history of facial keloid scarring. All the patients were informed about the procedure, including the mechanism of action, recovery, and potential side effects prior to the treatment, and informed consent was obtained.

2.2. Botulinum Toxin Preparation. A 50-unit vial of letibotulinum toxin A (Botulax; Hugel Inc., Chuncheon, Korea) was diluted to 2 units/0.1 mL with 2.5 mL of 0.9% sodium chloride. The solution was prepared in 15 units for each cheek and 3 units each for the nose, glabella, and supraeyebrow area.

2.3. Treatment Device. An FMR device (Potenza, Jeisys Medical Inc., Seoul, Korea) was used for the treatment. The device was coupled with the CP21 pumping tip designed for drug delivery. The tip consists of 21 microneedle electrodes with a diameter of 350 μm . All microneedles are insulated, except for the lower 0.3 mm, and the length can be adjusted from 0.5 to 2.5 mm, depending on the anatomical site. During the procedure, 6 W of monopolar radiofrequency energy was delivered locally from the microneedle with each shot. The FMR device delivered the drug through the pumping technique [13]. First, the needles penetrated the dermis, and the chamber entered a vacuum state. Next, the radiofrequency energy was delivered to the dermis, and the needles were ejected. The vacuum state was lost, and the resulting change in airflow pressure enabled the drug to penetrate the dermal layer.

2.4. Protocol. Patients underwent the treatment in two sessions: visit 1 (baseline) and visit 2 (4 weeks after the baseline). Patients were instructed to return to the clinic for two additional posttreatment evaluations at 8 weeks (visit 3) and 12 weeks after the baseline (visit 4). All patients received the same treatment regimen from a single dermatologist.

Topical anesthetic cream (Encaïn®; a mixture of lidocaine 2.5% and prilocaine 2.5%; Kolma Korea Co., Seoul, Korea) was applied to the face 30 min prior to the treatment. The BTA solution was applied to erythematous lesions on the face by spraying with a 30-gauge insulin syringe immediately before operation with the FMR device. Then, drug delivery to the dermis was performed using the FMR device coupled with the CP21 pumping tip.

The FMR device was used with the following parameters: pumping mode, 1-MHz frequency; 1.0–1.5 mm micro-needle penetration depth; five to eight levels; and two to three passes. The area that was bleeding was wiped with saline-soaked gauze after the procedure. All participants were instructed to avoid potential triggering factors of rosacea such as the consumption of spicy or hot foods, excessive alcohol intake, and prolonged sun exposure during and after the treatment period. In addition, participants were advised to apply sunscreen regularly.

2.5. Clinical Assessment. A nontreating investigator evaluated the patients' facial erythema using the erythema index (EI), the clinician erythema assessment (CEA), and the investigator's global assessment (IGA). Images were obtained at each visit using the standardized photographic system Janus-I (PIE Co., Ltd., Suwon, Korea), which employs the digital camera Canon EOS 100 D (Canon Inc., Tokyo, Japan) to capture the entire face.

The EI was measured in the same cheek area at each visit using a spectrophotometer (Cortex Technology, Hadsund, Denmark). The photodetector was used to compute the index by measuring the absorbed and reflected light at a wavelength of 655 nm. The probe was applied to the skin surface in a room with constant temperature (20–24°C) and humidity (28–38%).

CEA is a standardized grading system used to assess erythema severity [14]. After the follow-up period, the investigator was shown the patients' photographs taken at each visit and was asked to assess the severity (0 = absent, 1 = almost clear, 2 = mild, 3 = moderate, and 4 = severe) while being blinded to the chronological order in which the photographs were taken.

IGA was used to evaluate the overall efficacy of the treatment. The investigator was asked to compare the photographs of visits 2 to 4 with that of visit 1 and evaluate the treatment efficacy (0 = no improvement, 1 = 0–10%, 2 = 11–20%, 3 = 21–30%, 4 = 31–40%, 5 = 41–50%, and 6 = 51–100%).

Patient satisfaction regarding improvements in erythema and associated symptoms (1 = not satisfied, 2 = less satisfied, 3 = quite satisfied, 4 = satisfied, and 5 = very satisfied) was also assessed at visit 3. The following side effects were assessed in all patients: pain, erythema, edema, muscle weakness, musculoskeletal pain, dry mouth, fatigue, headache, or eye disorders.

2.6. Statistical Analyses. To validate the importance of the difference among CEA levels at each visit, one-way repeated measures analysis of variance was performed. When analyzing the difference in CEA values between visits 1 and 4, we excluded missing data. To evaluate the treatment effect on EI, the difference between the EI values of visits 1 to 3 was analyzed through a paired *t* test. Statistical significance was set at $P < 0.05$. All statistical analyses were performed using IBM SPSS statistics (version 27.0; IBM Corporation, Armonk, NY, USA).

3. Results

3.1. Baseline Characteristics. Of the 20 patients, 13 were women and 7 were men, with an average age of 36.7 ± 9.94 years (range, 21–58). Eleven had Fitzpatrick skin type III, and nine had type IV. The patients were classified into four types of rosacea according to the National Rosacea Society's standard classification system. [15]. The most common type was erythematotelangiectatic rosacea, with 13 patients (65%) being thus diagnosed; the remaining 7 patients (35%) showed the features of erythematotelangiectatic and papulopustular rosacea. No patients were diagnosed with phymatous rosacea or ocular rosacea (Table 1).

3.2. CEA. The mean CEA scores at visits 1, 2, and 3 were 2.8 ± 0.75 , 2.7 ± 0.64 , and 2.1 ± 0.89 , respectively (Table 2). At the baseline, none of the patients had CEA levels of 0 or 1. Instead, eight (40%), eight (40%), and four (20%) patients had CEA scores of 2, 3, and 4, respectively. At visit 2, 1 patient achieved a CEA score of 1 (5%), whereas 5 (25%), 13 (65%), and 1 (5%) patient (s) achieved CEA scores of 2, 3, and 4, respectively. At visit 3, 5 (25%), 10 (50%), 3 (15%), and 2 (10%) patients had CEA scores of 1, 2, 3, and 4, respectively. At visit 4, 14 patients returned to the clinic, with 5 (35.71%), 6 (42.86%), and 3 (21.43%) patients achieving the CEA scores of 1, 2, and 3, respectively.

CEA levels were significantly more improved at visit 3 than at the baseline ($P = 0.018$). Furthermore, the average CEA level was significantly more reduced at visit 3 than at visit 2 ($P = 0.049$; Figure 1). At visit 4, CEA was significantly more improved than that at visits 1 ($P = 0.005$) and 2 ($P = 0.015$) but showed no significant difference compared to CEA at visit 3 ($P = 0.810$).

Representative facial photographs of the patients demonstrating improvements at each visit are shown in Figure 2.

3.3. EI. The mean EI measurements at visits 1, 2, and 3 were 18.95 ± 5.19 , 16.90 ± 4.99 , and 16.60 ± 6.24 , respectively. At visit 4, six patients had their EI values measured, and the mean EI was 16.00 ± 2.88 . Compared with that at the baseline, the mean EI at visits 2 ($P = 0.04$) and 3 ($P = 0.005$) showed a statistically significant decrease (Figure 3).

3.4. IGA. At visit 2, the mean IGA score was 4.00 ± 3.00 , indicating a 31–40% improvement. At visit 3, all patients showed improvements, with a mean IGA score of 4.90 ± 2.50 , and most patients showed an improvement of $\geq 51\%$. At visit 4, 14 patients visited the clinic, and their mean IGA score was 4.21 ± 1.78 , indicating that the therapeutic effect persisted even 8 weeks after the last treatment (Table 3).

3.5. Patient Satisfaction. At visit 3, the mean score was 4.3 ± 0.56 . Seven patients (35%) had a score of 5, twelve (60%) had a score of 4, one (5%) had a score of 3, and none had scores of 1 or 2.

TABLE 1: Baseline characteristics of the participants.

Variable	(%)
Age, mean (SD), y	36.7 (9.94)
Sex	
Female	13 (65.0)
Male	7 (35.0)
Fitzpatrick skin type	
III	11 (55.0)
IV	9 (45.0)
Rosacea type	
ETR	13 (65.0)
ETR + PPR	7 (35.0)
Erythema index, mean (SD)	18.95 (5.05)
CEA	
0	0 (0.0)
1	0 (0.0)
2	8 (40.0)
3	8 (40.0)
4	4 (20.0)

SD, standard deviation; ETR, erythematotelangiectatic rosacea; PPR, papulopustular rosacea; CEA, clinician's erythema assessment.

Eleven patients reported experiencing subjective symptoms such as a heating or burning sensation, itching, and stinging at the baseline, whereas the remaining nine did not report any symptoms. Moreover, all patients reporting subjective symptoms at the baseline experienced improvements.

3.6. Adverse Events. All patients reported temporary erythema and edema immediately after the treatment. However, these side effects resolved within 1–2 days. The patients reported minimal pain. None of the patients experienced immediate side effects, such as allergic reactions. No side effects were serious enough to discontinue treatment. None of the patients reported muscle weakness, dry mouth, fatigue, headaches, eye disorders, or musculoskeletal pain.

4. Discussion

Erythema is a key symptom of rosacea, and a recent consensus has designated fixed centrofacial erythema as the sole diagnostic criterion [16]. The visible manifestation of rosacea can greatly impact patients and more so than physicians anticipate. Patients often experience embarrassment, social anxiety, depression, and decreased quality of life (QoL) [17]. Among the signs and symptoms, erythema is recognized as substantially reducing QoL [18]. In addition, patient assessment of the treatment, which is based on the patient's perception, can be lower than the physician's assessment. This highlights the challenges in treating rosacea and the need for more effective treatments.

A rosacea classification system of four presentations called subtypes (erythematotelangiectatic, papulopustular, phymatous, and ocular) and one variant (granulomatous) was established in 2002, but its limitations were recognized as it did not accurately represent the presentation of patients. To address this, the ROSCO panel proposed a new classification system in 2017 that is based on patient features and

TABLE 2: Clinician's erythema assessment (CEA).

CEA	Visit 1 (n = 20)	Visit 2 (n = 20)	Visit 3 (n = 20)	Visit 4 (n = 14)
Mean \pm SD	2.8 \pm 0.75	2.7 \pm 0.64	2.1 \pm 0.89	1.86 \pm 0.74
0 (absent)	0 (0)	0 (0)	0 (0)	0 (0)
1 (almost clear)	0 (0)	1 (5)	5 (25)	5 (35.71)
2 (mild)	8 (40)	5 (25)	10 (50)	6 (42.86)
3 (moderate)	8 (40)	13 (65)	3 (15)	3 (21.43)
4 (severe)	4 (20)	1 (5)	2 (10)	0 (0)

CEA, clinician's erythema assessment; SD, standard deviation. Values are presented as numbers (%).

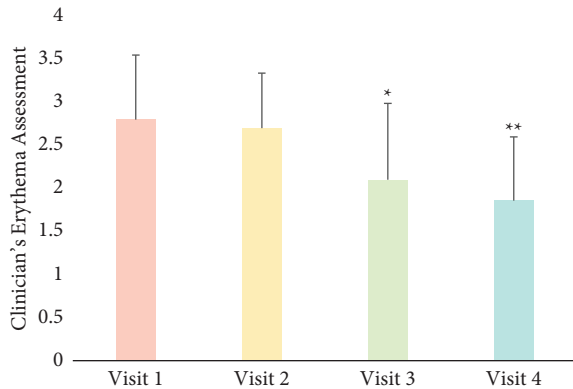


FIGURE 1: Mean clinician's erythema assessment (CEA). * $P < 0.05$ and ** $P < 0.01$, compared with the baseline.

encompasses the diversity of clinical presentations [16, 19, 20]. This new system includes persistent centropacial erythema with potential trigger factors as a diagnostic feature. This updated system allows for accurate characterization of individual patients and can optimize outcomes by highlighting the most bothersome features for treatment. Persistent erythema was the main symptom that caused distress to the patients included in our study. Considering the recent updated global perspective on rosacea diagnosis and classification based on a phenotype approach, our study was focused on erythema present in any of the four subtypes of rosacea. Even in patients with papulopustular rosacea, persistent erythema was the primary symptom at the time of treatment and inflammatory papules and pustules were mainly present in small numbers in areas of erythema. Therefore, we applied the same treatment approach to areas of erythema that exhibited inflammatory papules or pustules.

Recent molecular and morphological studies have revealed that neurovascular and neuroimmune aspects play a central role in the pathophysiology of rosacea [21]. Immunohistochemistry and gene array analysis revealed that patients' neuropeptide-encoding genes, such as vasoactive intestinal peptide (VIP) and pituitary adenylyl cyclase-activating polypeptide, were upregulated [22]. Moreover, the levels of mast cells, which are a potent contributor to the release of inflammatory and vasoactive mediators, are reportedly elevated in patients with rosacea [21]. In addition, dysesthesia, such as burning, pain, or itching, suggests the involvement of neurogenic inflammation in rosacea.

BTA inhibits the exocytosis of preformed vesicles in cholinergic nerves by cleaving the synaptosomal-associated protein 25 kDa at nerve terminals and reducing the secretion of acetylcholine [23]. Therefore, it can reduce erythema and flushing by inhibiting the cutaneous cholinergic vasodilatory system. In addition, BTA is known to modulate the secretion of inflammatory neuropeptides, such as VIP, substance P, and calcitonin gene-related peptide, and inhibit the expression of transient receptor potential vanilloid 1, all of which contribute to vasodilation and neurogenic inflammation [23–26]. Therefore, BTA not only alleviates erythema by reducing the levels of these mediators but also contributes to the reduction of inflammation and pain. Moreover, murine studies have demonstrated that BTA substantially decreases mast cell degranulation [27]. As a result of these functions, BTA helps improve erythema in rosacea.

To the best of our knowledge, this study demonstrated for the first time that the new treatment approach using transdermal delivery of BTA using FMR is safe and effective for improving erythema in patients with rosacea. Our treatment regimen was hypothesized to achieve the following effects: mechanical efficacy via needle penetration, radiofrequency energy, and drug response. According to the physician's evaluation, the CEA levels significantly improved at the third visit, which took place 4 weeks after completion of both treatment sessions. The EI also showed a significant decline at both the second and third visits. Moreover, physician-assessed CEA and IGA indicated that the therapeutic impact was sustained at 8 weeks after the last treatment. Subjective symptoms such as flushing, burning, itching, and stinging sensations also showed overall improvements. The patients were highly satisfied with their treatment and tolerated it well, considering its safety profile and resulting adverse events. In addition, the level of pain during the procedure was reportedly minimal.

Favorable clinical results of BTA have been reported for the treatment of facial erythema and flushing [4, 8, 28] and specifically rosacea [5, 6, 29, 30]. Previous trials of BTA for rosacea have not reported any important adverse effects. However, in the real-world setting, patients often experience pain during the procedure and are concerned about direct dermal injections. Our study employed FMR and the pumping technique to facilitate drug delivery while minimizing discomfort during the procedure. Therefore, we attempted a new treatment approach for the transdermal delivery of BTA by using FMR in this study and demonstrated impressive treatment outcomes. The procedure was

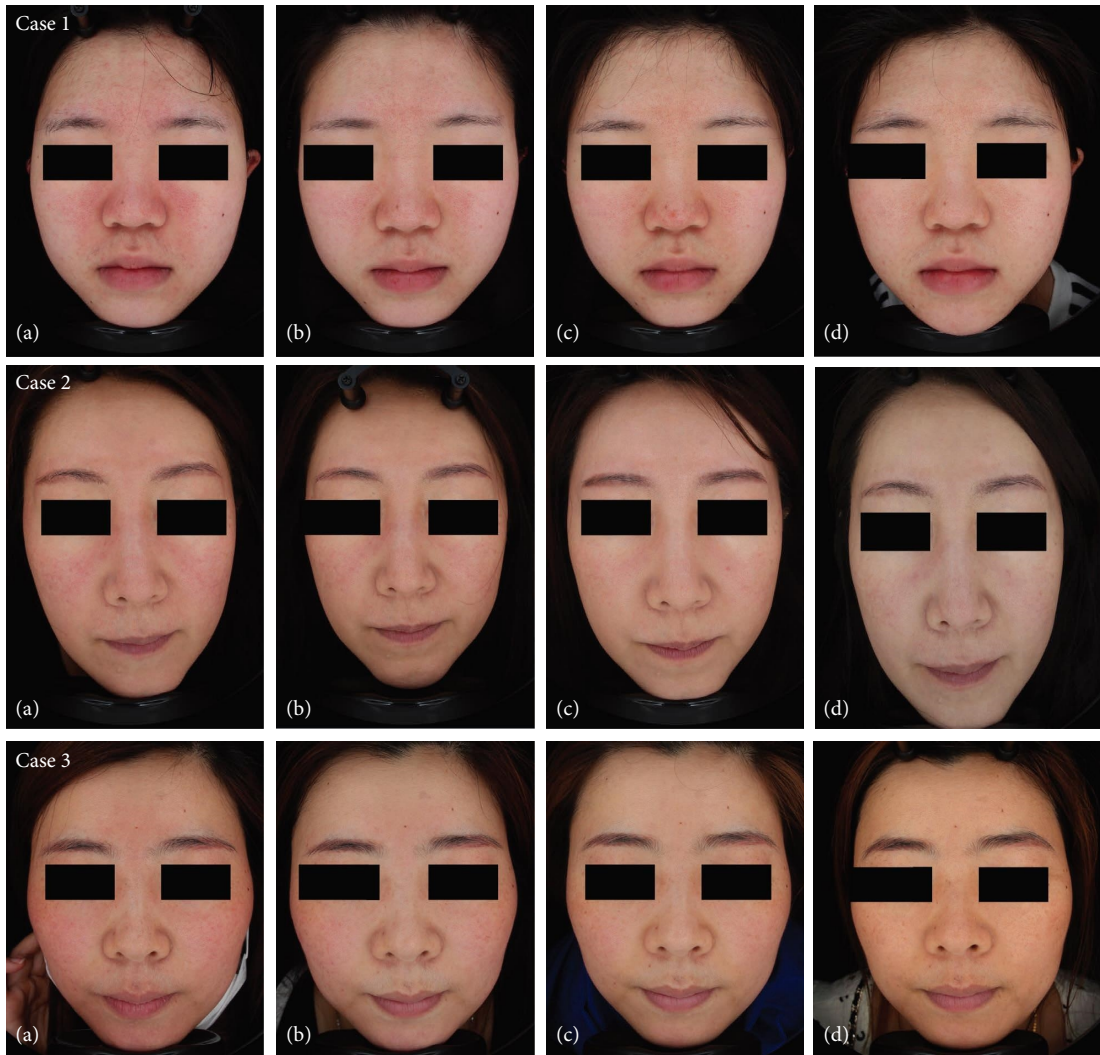


FIGURE 2: Representative patients' clinical photographs. Photographs were taken at visits 1 (a), 2 (b), 3 (c), and 4 (d). Case 1: A 21-year-old woman with erythema on the cheeks, nose, and supraeyebrow area. Her baseline clinician's erythema assessment (CEA) score was 4, which decreased to 2 at visits 2–4. Case 2: A 42-year-old woman with erythema on the cheeks, nose, and supraeyebrow area. Her initial CEA score was 3, remained the same at visit 2, and decreased to 2 at visits 3 and 4. Case 3: A 37-year-old woman with erythema on the cheeks, glabella, and supraeyebrow area. Her baseline CEA score was 4, which decreased to 3 at visit 2, 2 at visit 3, and 1 at visit 4.

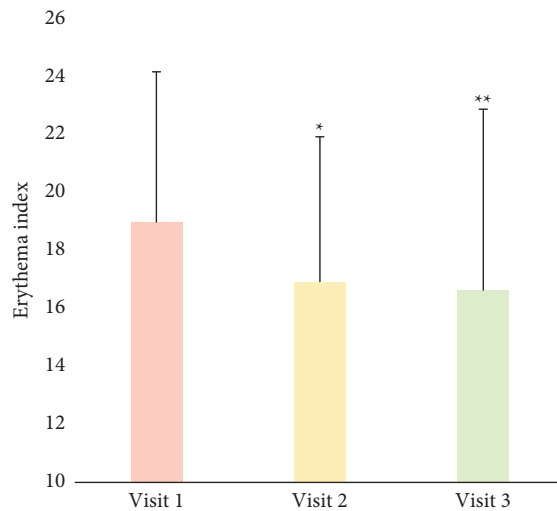


FIGURE 3: Mean erythema index. * $P < 0.05$, ** $P < 0.01$ compared with the baseline.

TABLE 3: Investigator's global assessment (IGA).

IGA	Visit 2 (n = 20)	Visit 3 (n = 20)	Visit 4 (n = 14)
0 (no improvement)	1 (5.00)	0 (0.00)	0 (0.00)
1 (0–10%)	1 (5.00)	1 (5.00)	1 (7.14)
2 (11–20%)	2 (10.00)	1 (5.00)	2 (14.29)
3 (21–30%)	4 (20.00)	2 (10.00)	3 (21.43)
4 (31–40%)	3 (15.00)	2 (10.00)	1 (7.14)
5 (41–50%)	3 (15.00)	3 (15.00)	1 (7.14)
6 (51–100%)	6 (30.00)	11 (55.00)	6 (42.86)

IGA, investigator's global assessment. Values are presented as numbers (%).

minimally painful, and no concerning side effects were reported.

FMR is primarily employed as a treatment option for acne scars, enlarged pores, and wrinkles [31]. Dermal structural remodeling, including neocollagenosis and ne-elastogenesis, is promoted by delivering radiofrequency energy to the dermis using microneedles. In addition, researchers in a few studies have used FMR to treat rosacea. In one clinical trial, a modest improvement in rosacea was achieved with FMR [10]. Erythema, flushing, and subjective symptoms were reduced, and the effect was maintained until 2 months after the last treatment. The mechanism through which FMR affects rosacea remains unclear. Reduction of sebaceous gland activity through dermal structure remodeling and thermal effects, as well as anti-inflammatory and antiangiogenesis effects, suppression of the overactivated innate immune system, and decreased mast cell levels, likely contribute [12]. After two sessions of FMR treatment, skin biopsy samples from individuals with rosacea have shown a significant reduction in the levels of mast cells and markers such as the vascular endothelial growth factor (VEGF), nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B), interleukin-8, interleukin-37, toll-like receptor-2 (TLR-2), and transient receptor potential vanilloid (TRPV)-2, -3, and -4 [10], which are known to contribute to development of rosacea [32].

The limitations of this study include the small sample size, short follow-up period, and absence of a control group. The effects in an RF alone group and a group in which RF and BT are combined need to be compared relative to a control group. This study lacks the long-term follow-up of patients necessary to assess the duration of the improvement and the possible occurrence of relapses. Furthermore, future studies must determine the specific details of the treatment protocol, such as the concentration of BTA, the parameters of FMR treatment, and the number of treatment sessions, to achieve improved treatment outcomes.

5. Conclusions

The novel therapeutic regimen of transdermal delivery of BTA using FMR may be an effective and safe strategy for managing erythema in rosacea.

Data Availability

The datasets analyzed during the current study are only available from the corresponding author upon reasonable request.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

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