



Efficacy and safety of non-insulated fractional microneedle radiofrequency for treating difficult-to-treat rosacea: a 48-week, prospective, observational study

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Received: 23 March 2021 / Revised: 5 June 2021 / Accepted: 10 June 2021

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Abstract

Rosacea is a common chronic facial inflammatory skin disease. However, treatment for “difficult-to-treat rosacea” cases has not been established. This 48-week, prospective, observational study analyzed patients who underwent three non-insulated fractional microneedle radiofrequency (NFMRF) sessions at 2-month intervals. Therapy efficacy, epidermal barrier function, and side effects were evaluated. 34 subjects completed the trial. NFMRF resulted in CEA score reduction from 2.65 ± 0.59 to 1.56 ± 0.50 ($P < 0.001$) and mean DLQI reduction from 16.70 ± 3.55 to 10.48 ± 2.92 ($P < 0.001$). The successes of CEA (44.12 vs. 2.94%), IGA (91.67 vs. 25.00%), and flushing (58.82 vs. 26.47%) were observed. Among 34 patients, 22 reported “excellent” or “good” improvement and 30 were “very” or “relatively” satisfied. Skin barrier results revealed that hemoglobin content significantly decreased from 376.47 ± 71.29 at visit 0 to 161.32 ± 52.86 at visit 3. 2 of 30 patients followed-up at 6 months had a relapse at 18 and 20 weeks, respectively. No serious side effects were observed. NFMRF alone results in visible improvement and has great efficacy for difficult-to-treat rosacea without compromising patient safety or damaging the skin barrier.

Keywords Rosacea · Difficult-to-treat rosacea · Non-insulated fractional microneedle · Radiofrequency · NFMRF · Epidermal barrier function

Introduction

Rosacea is a common facial skin disorder that often affects patients’ esthetics and mental health. It mainly manifests as persistent erythema, which may develop into phymatous changes, and can be accompanied by other clinical features

such as paroxysmal flushing, papules, pustules, and telangiectasia [1]. The prevalence of the disease is higher in the Western population and relatively lower in the Asian population with Fitzpatrick III–V [2, 3]. At present, the evaluation system in the 2017 diagnostic consensus [1] and “rosacea tracker” updated in 2019 [4] comprehensively assesses the degree of rosacea and can be used to better evaluate the disease severity and quality of life of patients.

Currently, treatments for rosacea are relatively limited, mainly including oral doxycycline or isotretinoin for papules and mild hypertrophy, and topical vasoconstrictors such as brimonidine, intense pulsed light (IPL) and vascular lasers for erythema and telangiectases [5]. However, some patients respond poorly to these treatments or experience frequent relapses; these patients are considered to have “difficult-to-treat rosacea [6]”. In addition to feeling insecure about their appearance, patients may have sensitivities resulting in burning and tingling sensations, which can disrupt their social life and lower their quality of life.

Radiofrequency (RF) is a nonionizing electromagnetic radiation with high potential for skin penetration, and it is a

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safe treatment for patients with darker skin types [7]. Non-insulated fractional microneedle RF (NFMRF) is applied by mechanically puncturing the deep dermis to form miniature radiofrequency thermal zones (RFTZs) with a diameter of 0.15–3 mm; it causes less damage to the epidermal layer and is widely used for skin tightening, wrinkle reduction, skin pore contraction, and acne scar reduction [8]. Microneedle mechanical stimulation and thermal effects in RFTZs can promote the secretion of multiple cytokines, reduce the microbial content in sebaceous glands of the hair follicle, and relieve local skin inflammation [9]. A previous split-face clinical trial reported that fractional microneedling radiofrequency (FMR) treatment showed modest clinical and histological improvements in general rosacea [10], and other studies suggested that FMR could improve acne-related post-inflammatory erythema [11]. Thus, we speculated that NFMRF may be a potential treatment for difficult-to-treat rosacea and aimed to investigate its efficacy and safety in this study.

Patients and methods

Study design

This was a prospective observational study included 35 patients with difficult-to-treat rosacea. Eligible patients were recruited 2 months before trial initiation. The study commenced in March 2018 and was completed in October 2019. The patients only received three NFMRF treatment sessions without any other combined treatment, and were examined at baseline/screening (visit 0) and at weeks 8 (visit 1), 16 (visit 2), and 24 (visit 3). Each treatment was performed at 2-month intervals. They were followed-up for a total of 24 weeks. The last treatment effect was evaluated before each treatment, and the final efficacy was evaluated at 2 months after the third treatment (visit 3) by an independent certified dermatologist. At the 6-month follow-up, patients were followed-up via face-to-face conversations to assess recurrence. The study was conducted in accordance with the Declaration of Helsinki and local laws and regulations and approved by the Ethics Committee of Xiangya Hospital, Central South University. All participants provided written consent.

Treatments

Before each treatment, the participants were regularly received face cleansing and topical anesthetic drugs were not used. All patients received treatments using a non-insulated microneedle radiofrequency system (Intensif applicator, EndyMed, Caesarea, Israel). The treatment site was the entire red area on the face, and the operating parameters

were as follows: depth, 2.5 mm; pulse width, 110 ms; overlap rate, 10%. Energy fluctuations of 6–12 w were adjusted according to local swelling and pain during the operation. The endpoints of the procedure were mild erythema, mild swelling, and whitening of the epidermis at the treated sites. Patients were advised to routinely use skincare products (Crème peaux intolérnates, Avene Co., France) and sunscreen during the study. High-resolution photographs were acquired using VISIA-CR (Canfield Scientific Inc., Fairfield, NJ, USA). The Skin analysis SHP88 system (Courage + Khazaka electronic GmbH, Germany) was used for epidermal barrier function evaluation.

Study participants

Participants were recruited from a group of rosacea patients treated for more than 2 years at our center, and they met the criteria of the 2017 diagnostic consensus [1]. They had obvious erythema or papules, with flushing and discomfort despite repeated treatments. Difficult-to-treat rosacea was defined as rosacea resistant to at least 3 months of cycline use or 6 months of isotretinoin use combined with topical brimonidine application or IPL within the last 1 year, or rosacea that frequently relapsed (relapse within 2 months after treatment, with ≥ 3 relapses). Due to the refractory symptoms of the patients, 15 of them received pathological biopsy of lesions to rule out the diagnosis of other diseases and confirm the diagnosis of rosacea. Patients aged ≤ 18 years, pregnant women, and patients with other facial skin or systemic diseases were excluded.

Endpoints

Primary endpoints were changes in the Clinician Erythema Assessment (CEA) score and Dermatology Life Quality Index (DLQI) after three treatments, relative to baseline values. The secondary endpoints were as follows: (i) decrease in the flushing global score in the week prior to each visit (medical history based on diaries kept a week prior to starting treatment); (ii) decrease in CEA and Investigator's Global Assessment (IGA) scores and decrease in dryness, stinging, and burning at each post-baseline visit; (iii) decrease in DLQI at each visit; and (iv) investigator's global improvement and patient's global satisfaction at each intermediate visit.

The other endpoints included the following: (i) percentage of patients with CEA success (CEA grading decreased to level 1 or below), flushing success (flushing grading decrease to level 1 or below), and IGA success (IGA grading decrease to level 1 or below); (ii) epidermal barrier function scores at each visit, including skin water content, oil content, melanin, hemoglobin, transepidermal water loss (TEWL),

and pH; and (iii) adverse events at each visit and pain sensation that was self-assessed by the subjects using a ten-point visual analog scale (VAS) scale, where 0 denoted “no pain” and 10 denoted “severe pain”.

Statistical analysis

Statistical analysis was performed using SPSS version 22.0 (SPSS, Chicago, IL, USA). Measurement data are presented as mean \pm standard deviation (SD) or median (range). For continuous variables, the analysis of variance test was applied to test the mean differences. The paired *t* test and Wilcoxon sign-rank test were used for the evaluation of differences in paired continuous data with normal and non-normal distributions, respectively. Categorical data are presented as an absolute number (with the percentage [%]), and between-group differences were tested using the chi-squared test. Descriptive analyses were performed for adverse events. *P* values of <0.05 were considered statistically significant.

Results

Subjects

In total, 35 participants were enrolled, and 34 completed the study (Table 1). All subjects had mild-to-severe erythema (CEA ≥ 2), with 5.88 and 52.94% exhibiting severe (CEA = 4) and moderate (CEA = 3) erythema, respectively. They had no pustules, but mild (IGA = 2) and moderate papules (IGA = 3) were found in 8.82 and 26.47% subjects, respectively. In addition, 50% subjects showed moderate or severe flushing (self-reported score ≥ 3), 64.71% reported significant burning sensations, and 38.2% reported skin stinging sensations. From these, five cases showed slight phymatous changes while nine showed edema. The previous therapies commonly included topical treatments (94.12%), tetracyclines (100.0%), isotretinoin (64.71%), and IPL therapy (35.29%).

Efficacy

Three NFMRF treatments decreased the average CEA score from 2.65 ± 0.59 to 1.56 ± 0.50 ($P < 0.001$), while two treatments decreased the average score to 1.68 ± 0.47 ($P < 0.001$). Thus, NFMRF showed potential for the rapid treatment of difficult-to-treat erythema. The average DLQI also gradually decreased with the number of treatments, with the mean values at visits 0 and 3 being 16.70 ± 3.55 and 10.48 ± 2.92 , respectively ($P < 0.001$). This suggested an obvious improvement in the patients' quality of life (Table 2).

Some other rosacea symptoms showed similar improvement after three NFMRF treatments. Self-assessed scores

Table 1 Baseline characteristics of 34 patients with difficult-to-treat rosacea

Characteristics	Outcomes
Age—Median (range) year	28 (21–50)
Sex—No. (%)	
Male	2 (5.88)
Female	32 (94.12)
Phototype ^a	
III	16 (47.06)
IV	18 (52.94)
Height—Median (range) cm	162 (150–182)
Weight—Median (range) kg	53 (40–71)
BMI ^b —Median (range) kg/m ²	20.27 (16.94–23.92)
Time since diagnosis—Median (range) year	3.5 (2–20)
Rosacea with melasma—No. (%)	4 (11.76)
Rosacea with dermographism positive—No. (%)	11 (32.35)
CEA ^c	
Level 2 (mild)	14 (41.18)
Level 3 (moderate)	18 (52.94)
Level 4 (severe)	2 (5.88)
IGA ^d	
Level 0 or 1 (clear or almost clear)	22 (64.71)
Level 2 (mild)	3 (8.82)
Level 3 (moderate)	9 (26.47)
Phymatous changes—No. (%)	5 (14.71)
Edema—No. (%)	9 (26.47)
Previous conventional therapy failures—No. (%)	27 (79.41)
Frequently relapsing—No. (%)	7 (20.59)

^aPhototypes III sometimes mild burn, tans uniformly; IV very rarely burns, always tans well

^bBMI body mass index

^cCEA clinical erythema assessment

^dIGA Investigator's Global Assessment

for flushing gradually decreased from 2.62 ± 0.69 to 1.35 ± 0.59 at visit 3 ($P < 0.001$), while burning sensations significantly reduced (5.35 ± 1.43 at baseline to 1.74 ± 1.46 at visit 3; $P < 0.001$). However, stinging sensations slightly decreased, with no statistically significant difference ($P = 0.296$). This could be attributed to the low self-scores at baseline. A high proportion of patients achieved CEA success (44.12 vs. 2.94% at visit 1, $P < 0.001$) and flushing success (58.82 vs. 26.47% at visit 1, $P = 0.007$) at visit 3. The initial 12 patients with refractory papules also achieved positive results; thus, there was a high proportion of subjects with IGA success at visit 3 (91.67 vs. 25.00% at visit 1, $P < 0.001$). Facial telangiectases ($P = 0.254$) and dryness ($P = 0.561$) showed insignificant changes (Table 2). Moreover, “excellent” or “good” improvement was reported by 22 of the 34 subjects (64.71%) at visit 3

and five (14.71%) subjects at visit 1 ($P < 0.001$). Thirty subjects (88.24%) were “very” or “relatively” satisfied at visit 3; this was significantly higher than the proportion

at visit 1 (14 subjects [41.18%]; $P < 0.001$; Fig. 1). The photographs of the subjects are shown in Figs. 2 and 3.

Among the 34 NFMRF responders at visit 3, 30 (88.2%) completed the 24-week follow-up. Erythema without

Table 2 Efficacy of NFMRF in treating 34 patients with difficult-to-treat rosacea

Outcomes	Visit 0	Visit 1	Visit 2	Visit 3
Phenotype				
Flushing	2.62 ± 0.69	1.94 ± 0.64	1.44 ± 0.55*	1.35 ± 0.59*
Fixed erythema	2.65 ± 0.59	2.44 ± 0.55	1.68 ± 0.47*	1.56 ± 0.50*
Telangiectases	1.30 ± 0.75	1.18 ± 0.78	1.18 ± 0.62	1.18 ± 0.66
Dryness	1.68 ± 1.76	1.71 ± 1.81	1.50 ± 1.44	1.53 ± 1.50
Burning	5.35 ± 1.43	3.71 ± 1.58*	3.03 ± 1.87*	1.74 ± 1.46*
Stinging	0.85 ± 1.26	0.71 ± 1.04	0.71 ± 1.15	0.68 ± 1.13
DLQI ^a score	16.70 ± 3.55	14.88 ± 3.14*	11.79 ± 3.94*	10.48 ± 2.92*
CEA success ^b		1 (2.94)	11 (32.35)	15 (44.12)**
Flushing success ^c		9 (26.47)	18 (52.94)	20 (58.82)**
IGA success ^d	12 (baseline)	3 (25.00)	7 (58.33)	11 (91.67)**

^aDLQI dermatology life quality index

^bCEA success CEA grading decrease to level 1 or below

^cFlushing success flushing grading decrease to level 1 or below

^dIGA success IGA grading decrease to level 1 or below

*vs visit 0, $p < 0.05$; **vs visit 1, $p < 0.05$

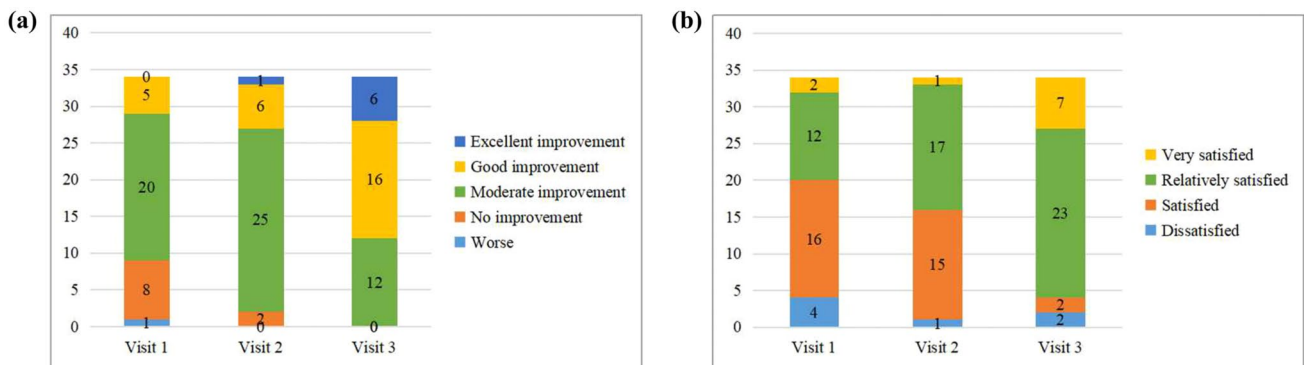


Fig. 1 **a** Investigator's Global Assessment of improvement at each intermediate visit for those patients who had 'excellent' or 'good' improvement. **b** Patient's Global Assessment of satisfaction at each intermediate visit for those patients who had 'very' or 'relatively' satisfied

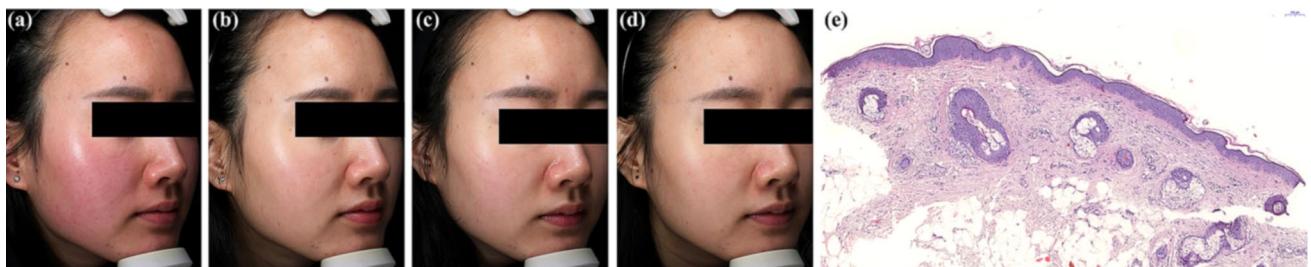


Fig. 2 **a–d** The photographs of a female subject with neurogenic rosacea at visits 0, 1, 2, and 3. **e** Histopathological examination showing the dilated blood vessels in the superficial dermal, with mild to moderate lymphocyte infiltration around the blood vessels (H and E, ×100)

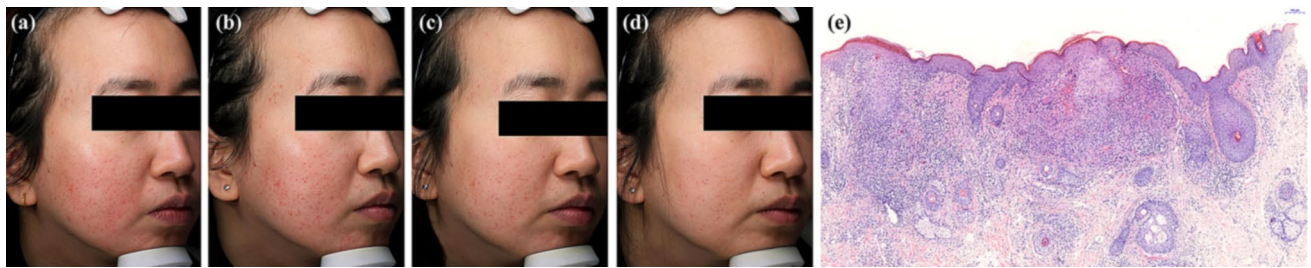


Fig. 3 a–d The photographs of a female subject with recalcitrant granulomatous rosacea at visits 0, 1, 2 and 3. e Histopathological examination showing infiltration of inflammatory cells around blood

vessels and hair follicles, epithelioid tissue cells and multinucleated giant cells constitute granuloma (H and E, $\times 100$)

intolerable discomfort relapsed in two (5.88%) patients at 18 and 20 weeks, respectively.

Epidermal barrier function

Then, the epidermal barrier function was evaluated by skin analysis SHP88 system. The hemoglobin level significantly decreased from 376.47 ± 71.29 at visit 0 to 161.32 ± 52.86 at visit 3 ($P < 0.001$). Other indicators, including the oil content, water content, melanin, TEWL, and skin PH, showed no obvious changes. Thus, NFMRF had minimal adverse effects on the skin barrier function (Table 3).

Safety

The incidence of NFMRF treatment-related side effects was extremely low. Most patients experienced little bleeding during the operation. The VAS score for pain was very low (average: 2.29 ± 0.82), which indicated that the procedure could be tolerated without the need for topical anesthesia. Four subjects reported minor, transient burning sensations and worsening of erythema; both symptoms subsided within 2 h. Other side effects such as post-inflammatory hyperpigmentation, epidermal burns, and scar formation were not observed.

Discussion

In this study, we investigated the efficacy and safety of NFMRF for difficult-to-treat rosacea and found that is a potentially effective and safe procedure. According to our clinical observations, we summarize the reasons for drug and treatment failures according to the patients' clinical features and treatment histories, and speculated difficult-to-treat rosacea cases can be mainly divided into two types: neurogenic rosacea and recalcitrant granulomatous rosacea (Table 4).

Some patients have unbearable burning sensations or flushing with or without severe erythema. Severe subjective signs that sometimes do not correspond to objective symptoms seriously affect the quality of life and social activities, and sometimes do not allow patients to sleep well. These patients may also show other psychological disorders such as anxiety and nervousness and are very vulnerable to emotional changes or external triggers. Some scholars consider these patients to have neurogenic rosacea [12]. Some researchers have proposed that oral antipsychotic drugs are effective in some patients [13], but these drugs may be unsuitable because of adverse effects such as extrapyramidal reactions. Moreover, patients may refuse to accept a diagnosis of a psychiatric disorder. Significant reductions in fixed erythema and flushing of neurogenic rosacea were observed after NFMRF in our study. These

Table 3 Epidermal barrier function index in the microneedle radiofrequency therapy

Outcomes	Visit 0	Visit 1	Visit 2	Visit 3
Oil content ($\mu\text{g}/\text{mm}^2$)	41.55 ± 34.30	37.88 ± 27.95	43.88 ± 30.55	37.16 ± 22.89
Water content	53.64 ± 26.61	48.63 ± 22.91	52.52 ± 22.38	57.15 ± 20.96
Melanin	138.96 ± 51.30	145.05 ± 47.55	134.89 ± 47.87	139.19 ± 47.52
Hemoglobin	376.47 ± 71.29	$303.82 \pm 69.63^*$	$233.59 \pm 64.16^*$	$161.32 \pm 52.86^*$
TEWL ^a ($\text{g}/\text{mm}^2 \text{ h}$)	13.09 ± 6.32	11.42 ± 5.01	12.49 ± 6.66	13.69 ± 5.51
pH	5.43 ± 0.36	5.44 ± 0.35	5.42 ± 0.33	5.42 ± 0.30

^aTEWL transepidermal water loss

*vs visit 0, $p < 0.05$

Table 4 The analysis of possible reasons for difficult-to-treat rosacea

Number of cases	Difficult-to-treat clinical features	Common treatment histories	Possible reasons
8	Recurrent severe flushing, erythema with edema	Topical brimonidine, oral doxycycline, IPL, oral antipsychotics (8 cases)	Neurogenic rosacea
4	Recurrent severe flushing with edema, mild erythema		
3	Intolerable burning, with flushing and erythema		
7	Frequently relapsing	Topical brimonidine, oral doxycycline, oral isotretinoin	
12	Persistent deep papules with or without phymatous changes	Oral doxycycline, oral isotretinoin	Granulomatous rosacea (pathologic diagnosis)

patients previously underwent multiple treatments for erythema and flushing, with poor results. We consider that the therapeutic mechanism of NFMRF may contribute to our successful treatment. Thermal energy is directly delivered to the subcutaneous sites to reduce the secretion of inflammatory factors, such as NF- κ B and interleukin-8, and vascular endothelial growth factor (VEGF), thus controlling skin inflammation and vascular abnormalities [10, 14]. This can directly coagulate the deeper blood vessels and reduce the number of blood vessels, thereby controlling erythema. Most patients with neurogenic rosacea were troubled by an unbearable burning sensation, and their self-scoring showed an obvious improvement in symptoms after the treatment. There may be other possible therapeutic targets for rosacea, such as heat from RF, which may inhibit the expression of transient receptor potential vanilloid (TRPV) [15], reduce nerve discharge, and stabilize neural function [16] to relieve flushing and burning.

In some patients, most of the superficial papules and pustules subsided after the oral administration of doxycycline or isotretinoin, and erythema also decreased after IPL treatment. However, some deep follicular papules could not be removed by any regular treatments. These papules are relatively hard to touch and show granulomatous changes in biopsy. This type is called recalcitrant granulomatous rosacea [17]. Previous reports revealed that some special treatments such as dapson [18], thalidomide [19], and chromophore gel-assisted phototherapy [20] could improve granulomatous rosacea. However, these treatments focus on controlling inflammation and may have major side effects, including drug hypersensitivity and hematological abnormalities. Considering the pathological characteristics of granulomatous changes, NFMRF could promote collagen rearrangement and balance the release and absorption of multiple matrix metalloproteinases [8, 21] other than those that control the vessels, thus reducing and controlling proliferation. Therefore, compared with drugs, NFMRF treatment has greater focus on comprehensive targets, which also provides clues for choosing a more comprehensive treatment plan.

Unexpectedly, in our clinical observation, we found that the skin texture and pores under dermoscopic guidance were improved after three treatments in some patients with swelling or edema (data not shown). This shows a normal skin repair ability and the partial ability to resolve edema and restore the skin barrier function [22, 23]. Swelling induced by the lymphatic circulation lacks effective targets in the treatment of rosacea. This finding provides some clues for the subsequent treatment of lymphatic-associated edema, but further research on its possible mechanism is needed. Nasal swelling or hypertrophy in most patients also improved at the early stage, and it can be further confirmed that NFMRF can improve early abnormalities in the skin vasculature [24].

With regard to the skin barrier function, we found no significant reduction in the oil content. This result is different from that after FMR treatment for rejuvenation, which reduces the oil content [25]. The low energy used in NFMRF could be a contributing factor. Overall, the skin's water and oil balance showed no significant change [26], which suggested that NFMRF causes very little damage to the epidermal barrier. While controlling dermal inflammation, NFMRF can be combined with a reasonable and scientifically proven skincare regimen to reduce recurrence and improve treatment efficacy.

However, a previous study reported that FMR could induce rosacea symptoms in patients undergoing treatments for cutaneous wrinkles [27]. In rejuvenation treatments, the RF energy is relatively high. High RF energy is associated with the following conditions. First, the subcutaneous temperature needs to reach a certain temperature to induce collagen reconstruction, but this temperature may also be the threshold temperature for activating the TRPV channel [28, 29], which could trigger symptoms such as facial flushing and burning. Second, the high energy will inevitably cause pain in patients and necessitate the external application of anesthetics, which, along with the thermal energy, can aggravate rosacea by leading to an imbalance in the skin barrier function [30]. Third, because of the non-selective dispersion of RF energy, even if thermal energy is released subcutaneously to protect

the epidermis, the high energy may still influence the epidermis and cause skin barrier dysfunction. Therefore, in NFMRF for rosacea, selection of the appropriate RF energy requires a certain level of clinical experience. In general, we believe that patients can bear the pain caused by low-level energy treatment without topical anesthesia and show no obvious whitening of the epidermis and a low overlap rate (completely different from the rejuvenation treatment), which is beneficial for reducing the risk of rosacea exacerbation. In fact, other photoelectric treatments may also aggravate or induce rosacea. Thus, further studies are warranted to determine the appropriate energy parameters for various photoelectric treatments.

The limitation of this study is its small sample size. A multicenter, large-sample clinical trial is needed to validate our findings. Given that all subjects were diagnosed with difficult-to-treat rosacea and had undergone first-line treatments, the study lacked an effective control group, which is a shortcoming of an open-label trial. Moreover, the mechanisms of the two types of rosacea are different; thus, further investigations about their mechanisms are needed to determine their respective therapeutic targets.

Conclusions

NFMRF alone may result in visible improvement and show high effectiveness in the reduction of flushing, erythema, papules, and facial burning in patients with difficult-to-treat rosacea, without compromising safety or damaging the epidermal barrier. Thus, NFMRF could be a good alternative therapy for difficult-to-treat rosacea. Further studies should focus on optimizing the parameters and investigating combination therapies involving other medications or treatments.

Acknowledgements Thanks for Technician Xing Yang, Rong Ding, Jing Yao, Xuan Liu, and Bo Xu at Department of Dermatology, Xiangya Hospital, Central South University. The patients in this manuscript have given written informed consent to publication of their case details. We would like to thank Editage (www.editage.cn) for English language editing.

Author contributions All authors contributed to the study conception and design. Material preparation was performed by BW, YD, JL, and DJ. Data collection was performed by BW, PL, and YD. Analyses were performed by BW and SY. The first draft of the manuscript was written by BW and DJ. All authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Funding This work was supported by grants from the National Natural Science Foundation of China (81974480, 81874246).

Data availability Data were included as a supplementary material.

Code availability Not applicable.

Declarations

Conflict of interest All the authors declare that they have no conflict of interest. None of the authors received fees from Endymed or Avene Laboratories.

Ethical approval The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The detailed protocol of this study was approved by the Institutional Review Board of Xiangya hospital, Central South University.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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