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REPORT

Therapeutic effects of a new invasive pulsed-type bipolar radiofrequency for facial erythema associated with acne vulgaris and rosacea

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ABSTRACT

Facial erythema from rosacea and acne is one of the most common problems encountered in dermatologic clinics. Effective therapeutic interventions for persistent erythema, which can cause patients frustration and psychological distress, are needed. The aim of this study was to evaluate the efficacy and safety of an invasive short pulsed-type bipolar radiofrequency device (IPBRF) for the treatment of intractable facial erythema. Thirty-one patients who had been diagnosed with rosacea or acne vulgaris and combined erythema underwent at least two IPBRF treatment sessions (maximum: 5) at 2-week intervals. Treatment outcomes were evaluated by investigator global assessment (IGA) based on clinical photographs, patient global assessment (PGA) score, and skin biophysical parameters including erythema index (EI), melanin index (MI), and transepidermal water loss (TEWL). Most patients showed significant clinical improvement. IGA scores for erythema, pores and smoothness improved after treatment. PGA also showed a trend toward improvement. Mean EI was significantly improved after the second treatment compared to baseline, which maintained until the study period. MI and TEWL showed a tendency toward improvement. There were no serious adverse events reported during the study. IPBRF led to rapid clinical improvement in facial erythema associated with rosacea and acne vulgaris and could be an effective and safe treatment option.

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KEYWORDS
Radiofrequency; Erythema; Acne; Rosacea

Introduction

Facial erythema occurs in a variety of inflammatory skin diseases and is one of the most common problems encountered in dermatologic clinics. Although it may be temporary, many patients complain of persistent erythema, leading to frustration and psychological distress (1). Both rosacea and acne are relatively common and chronic inflammatory diseases for which effective therapeutic interventions are needed.

Previous studies investigated post-inflammatory erythema (PIE) treatment for rosacea and acne. Pulsed-dye laser (PDL) has been widely used, targeting hemoglobin and small-diameter vascular processes (2). PDL also activates endogenous porphyrins produced by *Cutibacterium acnes* (*C. acnes*) and may also have a photothermal effect similar to intense pulsed light (IPL). IPL has a wide-band light source that can ablate abnormal vessels of varying depths. Meanwhile, radiofrequency (RF) devices have emerged as therapeutic options because of their effects on dermal remodeling for rosacea and acne (3). The RF energy produced by electrical current allows direct energy transfer to deep tissue without or with minimal epidermal damage (4). It was initially developed for skin rejuvenation through the remodeling of collagen fiber, but its usage has expanded to the treatment of several dermatological diseases through anti-inflammation, anti-angiogenesis, and decreased sebaceous gland activity (5). Recently, pulsed-type, bipolar and alternating current RF using non-insulated microneedle electrodes have been implemented for more selective treatment effects.

The therapeutic effects of RF energy on rejuvenation (5) or acne scarring have been proven through several studies (4), but few studies have explored the effects of pulsed-type bipolar RF on post-inflammatory erythema associated with acne vulgaris and rosacea (3). The aim of this study was to evaluate the clinical efficacy and safety of this treatment for facial erythema associated with acne vulgaris and rosacea.

Method

A prospective clinical trial was performed at the Department of Dermatology of Hanyang University Hospital in Korea. The protocol and informed consent form were approved by the Institutional Review Board of Hanyang University Hospital. All patients were informed of the therapeutic benefits, risks, and possible complications before enrollment and provided written informed consent prior to any study-related procedures.

Subjects

Thirty-one Korean patients (26 females, 5 males, mean age 30.9 years, range 14–51; Fitzpatrick skin type: III or IV) were enrolled in the study between September 2016 and

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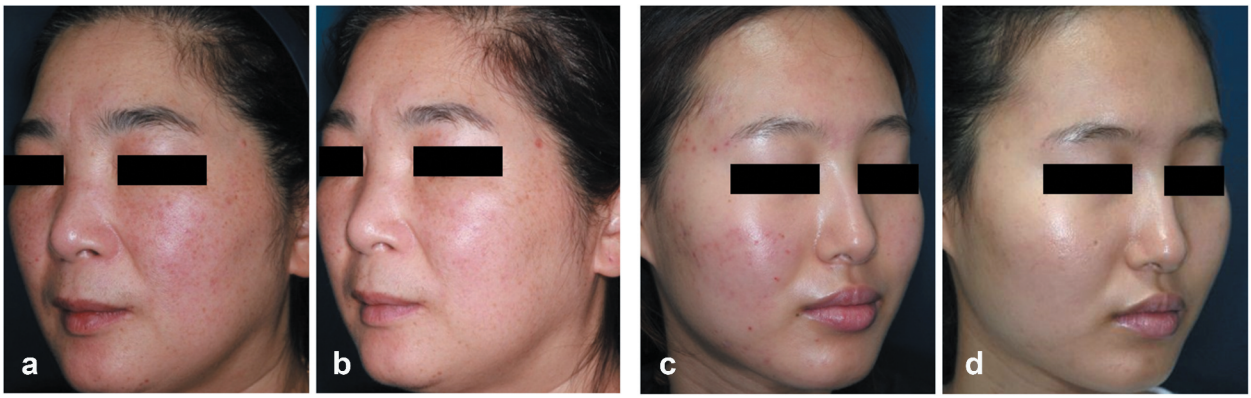

Figure 1. F/47, (A) baseline and, (B) post-treatment (3 successive treatments). Clinical photographs show apparent improvement of erythema. F/23, (C) baseline and (D) post-treatment (3 successive treatments). Clinical photographs show apparent improvement of erythema.

February 2018. All patients were clinically diagnosed with PIE associated with acne vulgaris or rosacea and combined erythema. The exclusion criteria were as follows: (i) a history of light or laser therapy during the previous 6 months; (ii) a history of treatment with systemic and topical antibiotics, intralesional corticosteroid injections, incision and drainage or surgical excision within the prior month; (iii) an implantable medical device including pacemaker, defibrillator, or leads; and (iv) active dermatologic disease such as connective tissue or autoimmune disease.

Description of devices and treatment protocols

The invasive short pulsed-type bipolar radiofrequency device (IPBRF) is a pulsed-type RF device used in bipolar mode at a frequency of 2 MHz. The device consists of a handheld applicator with a disposable single-use tip (Sylfirm®, Viol, Gyeonggi, Korea). The tip comprises 25 minimally invasive non-insulated microneedle electrodes/pins. The pins are arranged in a 5 (pins) x 5 (pins) pattern. With each electrodes 0.3-mm thickness, the distance between electrodes is 2 mm. The length of each pin is 10 mm, and the penetration depth can be adjusted from 0.5 to 3.5 mm. The amount of RF emission depends on the energy level, which is set from 1 to 10.

A topical anesthetic agent (2.5% lidocaine and 2.5% prilocaine; Anacin®, Cimic CMO, Bucheon, South Korea) was applied to the face under occlusion for 30 minutes when needed. Patients were treated with at least 2 sessions of IBPRFs (maximum: 5) at 2-week intervals over the entire face with the following settings: 2 or 3 passes at an intensity of 4 to 6, a penetration depth of 1.5 mm along the face and 1.0 mm along the forehead, with <10% overlap.

Clinical assessment

Investigator's global assessment (IGA) and patient global assessment (PGA)

Clinical photographs were taken at each time-point using identical camera settings, lighting, and patient positioning. At each treatment session, the overall efficacy of IPBRF was objectively assessed using the IGA compared with the baseline visit by two blinded physicians according to the following categories: 0 = clear, 1 = almost clear, 2 = mild, 3 = moderate, 4 = severe (6). Similarly, pores and smoothness were evaluated on a five-grade scale. In addition, patients were interviewed with regard to self-assessment of overall improvement compared to the prior visit, also on a five-grade scale: 0 = 'worse', 1 = 'no change', 2 = 'slight improvement', 3 = 'moderate improvement' or 4 = 'marked improvement'.

Skin biophysical parameters

Skin biophysical parameters including erythema index (EI), melanin index (MI), and transepidermal water loss (TEWL) were measured at each follow-up visit. EI and MI were measured using Mexameter MX18 (Courage Khazaka, Colgne, Germany), and TEWL was measured with a vapometer (Courage Khazaka, Colgne, Germany).

Safety assessment

The treatment site was visually inspected at each visit. Patients were queried about treatment-related adverse events, such as pain, tingling, bruising, edema, or irritation.

Statistical analysis

A mixed model for repeated measure analysis using Box-Cox transformation was used to compare differences in EI, MI, and TEWL between adjacent visits because the number of treatment sessions varied among patients. Post hoc analysis with Friedman's Test (R code) was used for the evaluation of IGA and PGA. A p-value ≤ 0.05 was considered statistically significant.

Results

Thirty-one patients who underwent at least two sessions of treatment were enrolled; among them, 18 patients completed a total of five treatment sessions. Most patients showed clinical improvement, as assessed by IGA and PGA score. An comparison between visits was conducted and the number of patients varied, so analysis was between adjacent visits.

Table 1. IGA for erythema, pores and smoothness. The highlights indicate statistical significance. Improvement in erythema appeared from the initial treatment. IGA for pores improved significantly between visit 2 and visit 4, and between visit 2 and visit 5 ($p < .0001$). Smoothness was significantly improved after two sessions ($p = .043$). The initial improvement in pores and smoothness was subtle, but was significant at the 4th and 5th visits.

Erythema	Visit (A)	Visit (B)	Mean Difference (A–B)	Standard Error	*P*-value
	1	2	.517	.112	<0.0001
		3	.966	.112	<0.0001
		4	1.224	.114	<0.0001
		5	1.340	.131	<0.0001
	2	3	.448	.112	.001
		4	.706	.114	<0.0001
		5	.823	.131	<0.0001
	3	4	.258	.114	.262
		5	.375	.131	.050
	4	5	.117	.132	1.000
Pore	1	2	.103	.091	1.000
		3	.310	.091	.009
		4	.559	.093	<0.0001
		5	.705	.107	<0.0001
	2	3	.207	.091	.250
		4	.455	.093	<0.0001
		5	.602	.107	<0.0001
	3	4	.248	.093	.089
		5	.395	.107	.003
	4	5	.147	.108	1.000
Smoothness	1	2	.034	.106	1.000
		3	.310	.106	.043
		4	.659	.109	<0.0001
		5	.895	.124	<0.0001
	2	3	.276	.106	.107
		4	.624	.109	<0.0001
		5	.861	.124	<0.0001
	3	4	.348	.109	.018
		5	.585	.124	<0.0001
	4	5	.236	.125	.627

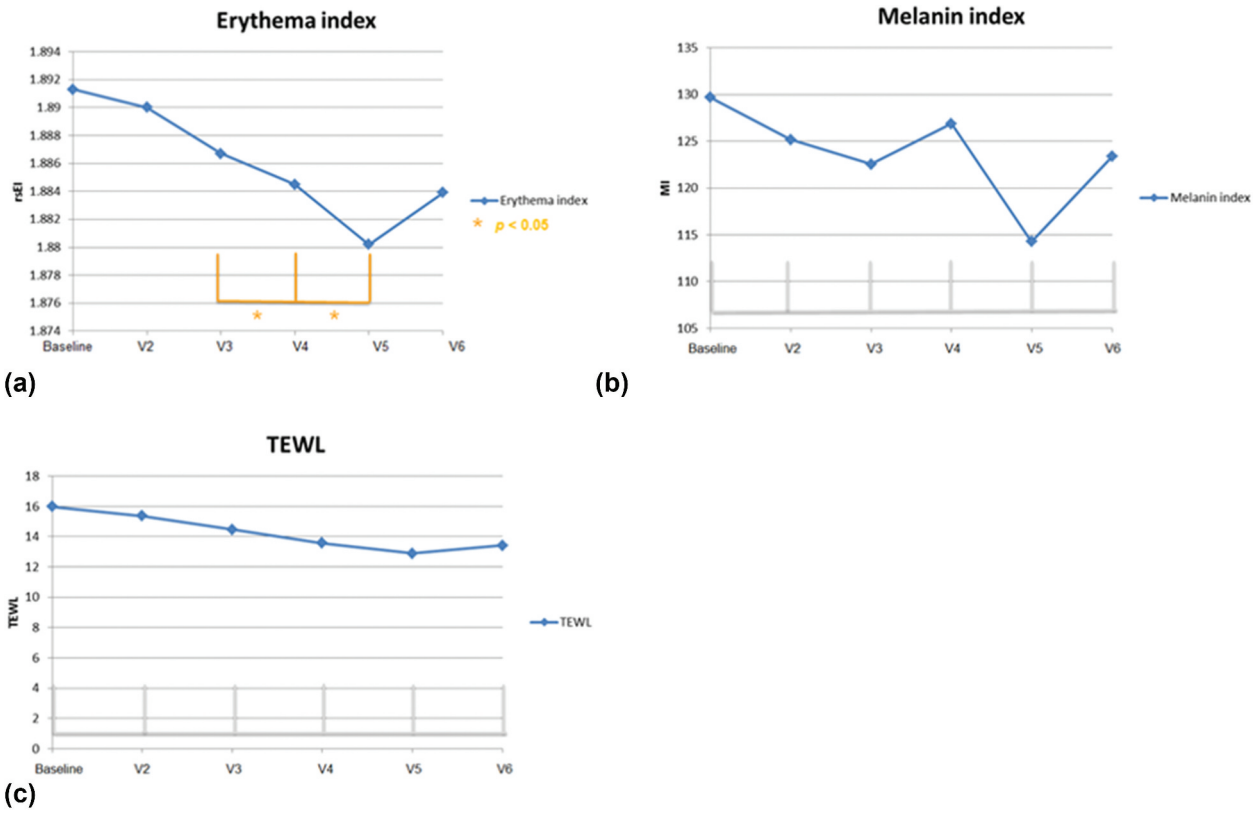

Figure 2. Change in (A) EI, (B) MI and, (C) TEWL during the treatment period. (Figure 2(A)): EI differed significantly between visit 3 and visit 4 (p<0.047) and between visit 4 and visit 5 (p<0.0005). (Figure 2(B)): MI also differed according to visit, but there was no significant difference between adjacent visits. (Figure 2(C)): The mean value of TEWL trended toward improvement with repetitive treatment, but this did not have a statistical significance. * rsEI value is the number converted to Box-Cox transformation.

Erythema was improved significantly even after just one treatment ($p < .0002$) and improvement was maintained until the sessions of treatment ($p < .0002$). Clinician assessment of erythema was significantly different between visit 1 and visits 2, 3, 4, and 5 ($p < .0001$), visit 2 and visit 3 ($p = .0001$), 4, and 5 ($p < .0001$). Thus, improvement in erythema appeared from the initial session. Improvement of pores and smoothness also appeared after 3rd and 4th treatment. Clinician assessment of pores improved significantly between visit 2 and visit 4, and also between visit 2 and visit 5 ($p < .0001$). Smoothness was significantly affected after two sessions ($p = .043$) and that effect was maintained until the last session (Table 1). The initial improvement in pores and smoothness was not dramatic, but was statistically significant at the 4th and 5th visits, indicating a delayed improvement in pores and skin texture. Subjective overall clinical improvements were evaluated by PGA. Mean PGA was 2.4 after the 1st treatment and 2.3 after the 2nd treatment, indicating slight to moderate improvement. Mean PGA after the 3rd, 4th and 5th treatment was 1.9, 1.8, and 1.5, respectively, suggesting greater improvement at the beginning of treatment and subsequent gradual improvement, similar to IGA.

EI gradually decreased at each visit, and was significantly different between visit 3 and visit 4 ($p < .047$) and between visit 4 and visit 5 ($p < .0005$) (Figure 2).

Post-treatment discomfort included transient pain, tingling, and immediate erythema, but these symptoms were mild and transient and improved within one or two days. Other treatment-related adverse effects such as pigmentary alterations, infection, and scarring were not observed.

Discussion

Facial erythema is a common result of acne inflammation and rosacea. Acne vulgaris is a common disorder of the pilosebaceous unit and acne patients usually complain of persistent erythema after inflammation. Rosacea is a disease accompanied by telangiectasia, erythema, flushing, or erythematous papules that is exacerbated by factors that result in dilated vessels. Inflammation is usually controlled by several anti-inflammatory medications; there is an increasing trend toward non-pharmacologic treatments due to antibiotic resistance and concerns about isotretinoins' teratogenic potential (7). Various treatment options including pulsed-dye laser therapy (1), IPL and RF devices have been used to treat rosacea and acne vulgaris.

Unlike monopolar RF, IPBRF using bipolar RF affects only the fractional microneedling radiofrequency zone, allowing the surrounding tissues to accelerate the wound healing process, resulting in a short recovery time. Moreover, newly developed pulsed-type RF differs from conventional continuous-type RF in that it transmits energy at very close intervals, thereby providing sufficient energy with less damage (8). The RF energy delivered by IPBRF restores epidermal barrier function, as confirmed in a previous study (9). In a previous experimental study of RF tissue reactions, RF-induced coagulation columns of thermal injury that were generated around each microneedle and concentrated maximally around the pointed tips of the electrodes in the dermis (10). Previously Na et al. reported that bipolar RF-induced tissue reactions were propagated preferentially along the outer layers of the dermal vascular components and perivascular structure in an *in vivo* micropig skin model (10). Continuous-type RF elicits a 'Na effect' (10) that conducts energy selectively to blood vessels, causing coagulation of vessels, but pulsed-type RF devices with a pulse width of a single pulse result in less epidermal injury and upper dermal vessel collapse but not destructed (10,11). Similarly, a decrease in proliferation of small blood vessels and perivascular inflammatory infiltration in the upper dermis was observed. Our EI values were significantly reduced after treatments. Several studies have suggested that rosacea is associated with vascular endothelial growth factor (VEGF)-mediated angiogenesis and lymphyangiogenesis (12) and that NF-kB, which activates IL-8 and VEGF expression, is chronically active in inflammatory disease including rosacea and acne (9). A previous study (9) reported that acne-related PIE improved with fractional microneedling radiofrequency (FMR) treatment, and suggested that after FMR treatment, NF-kB decreases and eventually reduces PIE by down-regulating the VEGF pathway. They showed reductions in IL-8, NF-kB and VEGF staining intensity after the second treatment session, and hypothesized that inflammation may contribute to neovasculogenesis, resulting in residual erythema after resolution of active acne lesions (9).

In this paper, to evaluate each aspect in more detail, our analysis compared adjacent visits. Clinician assessment of erythema improved significantly between visits 1 and visits 2,3,4,5 as well as between visit 2 and visits 3,4,5. This means that therapeutic response appears early and is maintained thoroughly to the end of the period. Pores and smoothness were also evaluated and exhibited significant improvement at later stages of treatment. This clinical improvement is consistent with previous studies (13), which suggested that fractional thermal injury of dermal collagen promotes new collagen, elastin, and hyaluronic acid formation to promote dermal remodeling. Ruiz-Esparza et al. suggested that the intradermal heating induced by RF not only facilitates dermal remodeling but also suppresses the activity of sebaceous glands (14). Active dermal remodeling is triggered by the chaperone HSP47 and led to the replacement of the radiofrequency thermal zone with new collagen by 10 weeks post treatment (13). Histologically reticular dermal volume, cellularity and elastin content also increased. In addition, the microneedle itself promotes migration of keratinocytes and fibroblasts, secretion of some growth factors and collagen synthesis (15). We observed that PIE improved immediately and dermal remodeling appeared as a delayed response, triggered by various RF-stimulated factors. When reviewing the treatment effects of our patients in this study, our patients with rosacea or acne erythema showed clinical improvement based on clinician assessment scale, PGA, and objective assessments with minimal downtime. In the case of erythema, objectively evaluated biophysical parameters were generally consistent with clinical evaluation. EI also showed significant differences between visits 3–4 and visits 4–5, indicating that improvement of erythema was sustainable after treatment. Considering both clinician assessment and objective biophysical parameters, this treatment appears to be effective after the third and fourth treatments in erythema

groups without other medications. The findings of this study can help to predict and explain the time course of treatment response to IPBRF in a clinical setting and serve as the cornerstone for extending the clinical applications of IPBRF with minimal post-treatment downtime. Patients complained of only mild pain and temporary erythema during and right after treatment. Therefore, IPBRF could be effective and safe in facial erythema patients, especially those who have darker skin types, like Asian patients.

However, this study has a number of limitations. First, there may be selection bias because the number of patients included was small. Clinically improved patients were satisfied and did not want further treatment, so the number of patients was different at each visit. Because the number of visits varied between patients, only adjacent visits were compared.

Despite these limitations, the present study is the first to show the efficacy of short pulsed-type IPBRF on PIE associated with rosacea or acne vulgaris. This study suggests that IPBRF could be an effective and safe adjacent option for treating facial erythema disorders. We found that improvement of erythema was maintained throughout the end of the period. At least 3 or 4 treatment sessions are needed to achieve dermal remodeling and clinical rapid improvement of erythema. Larger randomized, prospective studies of this therapeutic intervention are recommended to develop treatment protocols for facial erythema disorder.

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