Selective Sebaceous Gland Electrothermolysis Using a Single Microneedle Radiofrequency Device for Acne Patients: A Prospective Randomized Controlled Study

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Background and Objectives: The selective electrothermolysis of the sebaceous glands was suggested as a novel therapeutic option for facial acne. However, there has been no randomized controlled trial to evaluate the effectiveness and safety of the monopolar radiofrequency (RF) device using single microneedle with proximal insulation. The objective of the study was to evaluate the efficacy and tolerability of intralesional electrothermolysis using monopolar RF device and proximally-insulated single microneedle in acne patients.

Study Design/Materials and Methods: The prospective randomized controlled clinical trial was performed to treat moderate-to-severe facial acne. Subjects randomized to the treatment group received three treatments at 4-week intervals with an RF device, whereas the control group received micro-needling and extraction. For efficacy evaluation, reduction rate of acne lesions were evaluated by two independent physicians.

Results: Sixty-three patients completed the study and the results showed statistically significant improvement of inflammatory acne at 12 weeks. The number of inflammatory lesions was significantly reduced at 12 weeks (20.86 vs. −5.13; $P = 0.03$) compared with controls.

Conclusions: Selective sebaceous gland electrothermolysis can be a safe and effective method of achieving consistent improvement in acne. Lasers Surg. Med.

Key words: acne vulgaris; intralesional electrocoagulation; single-needle radiofrequency

INTRODUCTION

Acne vulgaris is one of the most common inflammatory skin diseases, characterized by the development of comedones, papules, and pustules. It may present with nodules and deep pustules that cause permanent facial scarring and associated negative social impact [1,2].

The pathogenic mechanism of acne vulgaris includes overactive sebaceous glands, the release of inflammatory mediators in the skin, follicular hyperkeratinization, increased and altered the sebum production under androgen control and follicular colonization by *Cutibacterium acnes* (*C. acnes*) [3]. Sebaceous glands and *C. acnes* colonization are central to the development of acne. Inflammatory processes involving lymphocytes and macrophages that stimulate pilosebaceous vasculature precede follicular hyperkeratinization [4]. Defective keratinocyte differentiation leads to the formation of comedones under the influence of androgens and to an increase of sebum lipid levels [5]. Sebaceous glands are a pivotal part of the immune system, producing various antimicrobial substances. Each sebaceous gland functions like an independent endocrine organ influenced by corticotropin-releasing hormone that might mediate the link between stress and acne exacerbations [3]. Sebaceous follicles containing a microcomedone provide an anaerobic and lipid-rich environment in which *C. acnes* flourishes [6]. Colonization of *C. acnes* follows initiation of sebum overproduction and inflammation.

Although many therapeutic options are available for acne vulgaris, relapse is common after stopping the treatments. In addition, treatments are often difficult and inconvenient to use, take a significant amount of time, and can be expensive, all of which contribute to the poor compliance [7]. Relapse rates after isotretinoin treatment are relatively low if the drug is administered with a sufficient cumulative dose of over 120–150 mg/kg [8]. However, it has some side effects such as cheilitis, xerosis, epistaxis, and increase in a liver enzyme and cholesterol levels. Teratogenic effects are also a major problem with the use of isotretinoin, especially in childbearing age [9]. For antibiotic treatment, an increasing concern is the upsurge of antibiotic-resistant bacteria [10].

Considering the pathology of acne, direct access to the sebaceous gland is necessary for an effective treatment. Thus, the selective destruction of the sebaceous glands

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could be an attractive treatment option. A previous report suggests that selective destruction of the sebaceous glands using the method proposed by Kobayashi [11] may represent an additional therapeutic option for facial acne. Although an anecdotal case series showed that an intradermal radiofrequency (RF) treatment can reduce the total count of inflamed glands [12,13], no randomized controlled trial was employed to evaluate the effectiveness of the single microneedle RF device. The objective of the present study was to evaluate the efficacy and tolerability of a single microneedle RF device in acne patients utilizing a 12-week, randomized and controlled trial design.

MATERIALS AND METHODS

Study Design and Patients Selection

The study was a single-center, randomized, evaluator-blinded, and placebo-controlled comparison clinical trial. The study was approved by the Chung Ang University Institutional Review Board (IRB No. C2014055(1251)), and a written informed consent was obtained.

All patients were between 18 and 40 years old, with moderate-to-severe acne vulgaris, as defined by an Investigator's Global Assessment (IGA) score (Table 1) and with Fitzpatrick skin types III–V. Exclusion criteria were use of oral isotretinoin for the treatment of acne within the previous 16 weeks, use of topical or systemic antibiotics within the previous 4 weeks, and pregnancy or lactation in female subjects. In addition, women using hormonal forms of contraception with anti-androgenic properties for 16 weeks were precluded from enrollment. All subjects were prohibited from using any anti-acne treatment except for standard washing and moisturizing procedures while participating in the study. A total of 66 patients with grade 3 and 4 of IGA scores were randomly assigned in a 1:1 ratio to RF device (33 patients) or control (33 patients). Baseline visits were used to obtain medical histories of each patient.

Treatment Protocols

A total of three treatments were administered at 4-week intervals. Before treatment, all subjects gently cleansed their faces with a mild cleanser, and then applied a topical anesthetic cream (EMLA; AstraZeneca Pharmaceuticals LP, Wilmington, DE). All patients were photographed at each visit. On each occasion, subjects were photographed by the same photographer in the same position, using an identical camera and lighting settings. The anesthetic was removed after 30 minutes and the subject was asked to adopt a supine position prior to the initiation of treatment. A 1-MHz RF device (AGNES®; AGNES Medical Co., Seongnam, Korea) was used for treatment. The antenna endplate was positioned beneath each patient's nape to set a monopolar circuit. A disposable, sterile insulated microneedle (I-type needle; AGNES Medical Co.) was fixed into the handpiece and then applied to ablate lesions. The microneedle was inserted into lesional follicular pores at an angle of 60–70° and a RF current was applied 1–2 times per lesion. Parameter settings were initially 4 W and 100 milliseconds and adjusted on the basis of clinical details. The day after treatment, contents of the comedo or inflammatory lesion were expressed by applying gentle pressure. In the control group, gentle needling with the same device and extraction of comedo was performed on lesions after administering topical anesthetic for 30 minutes. The treatment procedures in both the groups were performed on every acne lesions on the face. All adverse events were recorded and participant satisfaction was assessed using a seven-category scale with 1 representing "very dissatisfied"; 2, "dissatisfied"; 3, "somewhat dissatisfied"; 4, "indifferent"; 5, "somewhat satisfied"; 6, "satisfied"; and 7, "very satisfied".

Efficacy Evaluation

The primary outcome measure was the reduction rate of number of acne lesions at 12 weeks after treatment compared with a baseline. Two blinded dermatologists separately counted the number of participants' inflammatory acne lesions based on the digital photographs obtained at baseline, 4-, 8-, and 12-week follow-up visits. The reduction rate is the percent reduction in number of acne lesions from baseline.

Secondary outcomes measures included reduction rate of the number of acne lesions at 4 and 8 weeks,

TABLE 1. Investigator's Global Assessment (IGA) Scale

Rating	Definition
0 = Clear	Residual hyperpigmentation and erythema may be present
1 = Almost clear	A few scattered comedones and a few (<5) small papules
2 = Mild	Easily recognizable; less than half the face is involved Many comedones and many papules and pustules
3 = Moderate	More than half of the face is involved Numerous comedones, papules, and pustules
4 = Severe	The entire face is involved. Covered with comedones, numerous papules and pustules, and few nodules and cysts
5 = Very severe	Highly inflammatory acne covering the face; nodules and cysts are present

number of acne lesions at 4, 8, and 12 weeks, and reduction rate of the number of acne lesions rated by treating dermatologist at 4, 8, and 12 weeks. Follow-up patient satisfaction questionnaires were obtained at 4, 8, and 12 weeks.

Statistical Analysis

Statistical comparison between the treatment and control groups were performed using Wilcoxon's rank-sum test. Repeated-measured analysis of variance was used to compare reduction rates of acne lesions and patient satisfaction at each visit. The results are expressed as mean ± standard deviation, and $P < 0.05$ were considered statistically significant.

RESULTS

This study took place from October 12, 2016 to October 12, 2017. Sixty-six individuals consented and completed the first treatment session. Before the first efficacy evaluation, three patients dropped out of the study for personal reasons (Full analysis set [FA set]; Drop out—Treatment group: 2; control group: 1). An additional six patients discontinued the study and a total of 57 patients completed the study (Per protocol set [PP set]; Drop out—Treatment group: 2; control group: 4) (Fig. 1). In this study, FA set was used for analysis. The mean age of analyzed subjects was 23.41 ± 3.42 years and their ages ranged from 19 to 37 years. The group consisted of 42 men and 21 women. There were no significant differences in baseline acne lesion count ($P = 0.07$) and IGA score ($P = 0.20$) between two groups. Table 2 summarizes participant demographics.

A single microneedle RF device was significantly more effective than simple needling in treating acne lesions as measured by reduction rate and number of acne lesions at the 12-week follow-up. Mean reduction rate at the 12-week follow-up was $20.86 \pm 81.37\%$ in the treatment group and $-5.13 \pm 75.21\%$ in the control group ($P = 0.03$). The decrement in the mean acne count was 17.19 ± 27.97 in the treatment group and 3.17 ± 23.80 in the control group ($P < 0.01$) (Fig. 2). Representative clinical examples are shown in Figure 3. At 4 and 8 weeks compared with the control group, the reduction rate in acne lesions was insignificant. Mean reduction rate was $2.46 \pm 46.93\%$ in the treatment group and $1.32 \pm 68.81\%$ in the control group at 4 weeks ($P = 0.77$) and $24.22 \pm 41.18\%$ in the treatment group and $5.67 \pm 70.93\%$ in the control group at 8 weeks ($P = 0.28$). Further, no statistical differences in patient's satisfaction were identified between the two groups. The number and reduction rate of acne lesions evaluated by practitioners showed statistically significant differences between the treatment and control groups at every follow-up visit.

No serious adverse events were reported. Mild headache, upper respiratory infection, and dysmenorrhea, which were not associated with treatment, were reported by participants after the treatment.

DISCUSSION

This study demonstrates improvement in inflammatory acne after a series of three treatments with a single microneedle RF device compared with needling and extraction. Significant improvement from baseline was observed in acne reduction rate in the treatment group at 12 weeks compared with that observed in the control group. The number of acne lesions and the reduction rate at the 4- and 8-week follow-up examinations also tended to decrease significantly. No difference in patients' satisfaction was identified. Treatment-related adverse events were not observed.

Topical agents for acne, such as retinoids and antibiotics, need to be applied daily for several weeks and commonly cause skin irritation. Conventional oral medications, such as antibiotics, oral contraceptives, and isotretinoin, have significant side effects, including gastrointestinal trouble, antibiotic resistance, and teratogenicity, respectively [14–16]. Treating acne with laser or light-based modalities may be effective with fewer adverse effects than conventional therapy. A previous study found that photodynamic therapy (PDT) was the most well-founded treatment for acne using a laser and light device [16–18]. A laser or light device is thought to activate the photosensitizer, thus selectively damaging sebaceous glands and reducing *C. acnes*. Although PDT showed a therapeutic efficacy for acne, selective absorption of the photosensitizer by sebaceous glands was not enough to destroy the glands completely, which could lead to relapse.

The authors of the previous pilot study suggested that a single microneedle RF device has notable advantages over other acne treatment modalities [13]. As selective electrothermolysis results in the destruction of causative sebaceous glands, the relapse rate is lower. Additionally, this intervention achieves therapeutic efficacy in only two or three treatment sessions. Finally, when performed by properly trained therapists, the treatment is not associated with any severe side effects. The data of the present clinical trial is in accordance with that of the pilot study supporting those suggestions.

The RF procedures also have several characteristics that give them an edge over laser procedures. Intralesional electrocoagulation induces thermal coagulation zones around the pilocebaceous units via penetration of the microneedle through the epidermis and into target depth in the dermis. The length of the insulated and exposed part of the microneedle (500-μm proximally-insulated part on 1,500-μm microneedle) is designed to affect the sebaceous glands exclusively (Fig. 4). The T-shaped shoulder of the microneedle, which functions as a stopper provides uniform depth regardless across sessions and physicians.

The study has several limitations. First, the study period was too short to observe the long-term effectiveness of destroying sebaceous glands. An additional improvement is possible at intervals longer than 12 weeks. Previously, Lee [13] demonstrated effectiveness of a RF

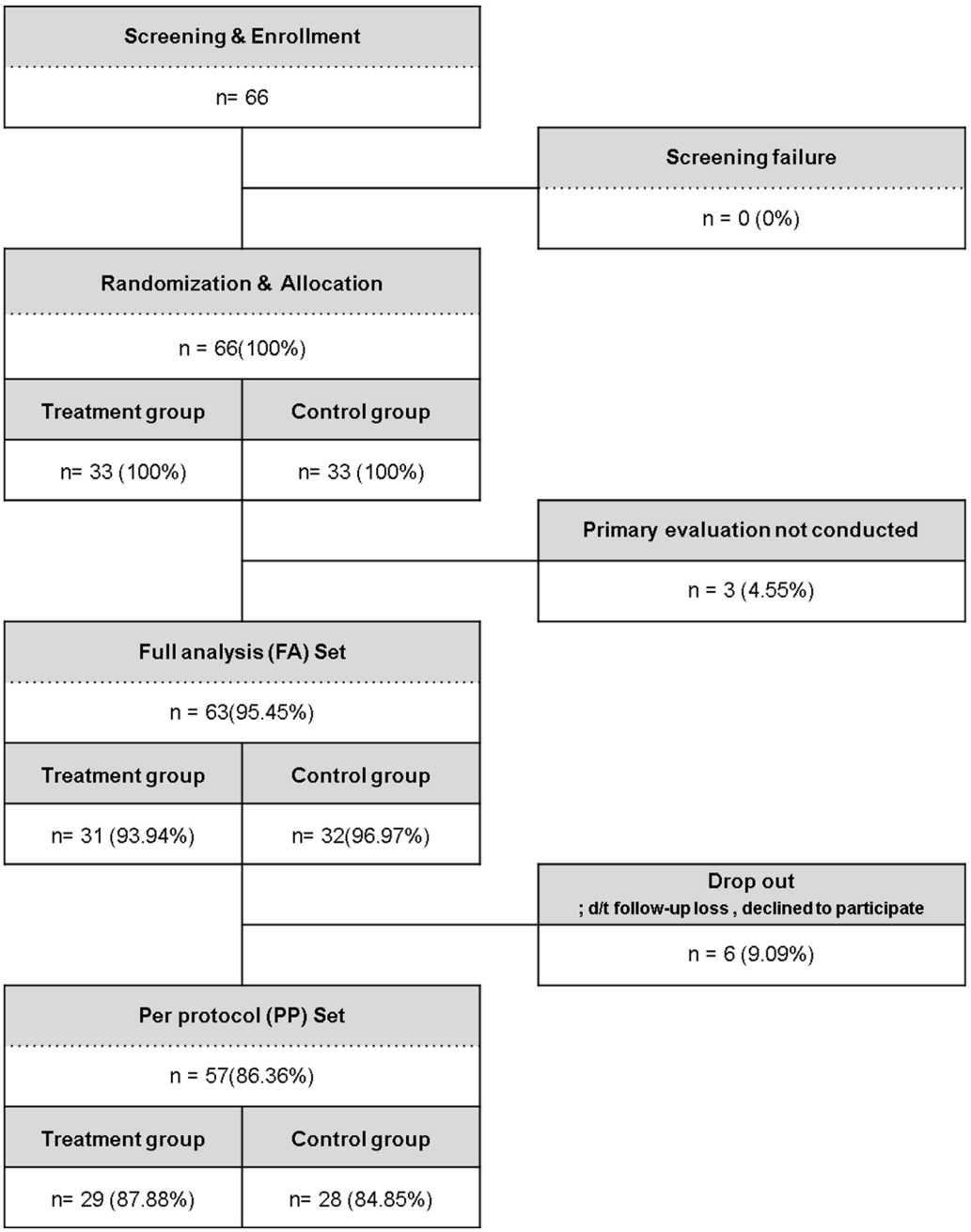

Fig. 1. Flowchart showing the study design.

TABLE 2. Demographic Characteristics of the Participants at Baseline (Mean ± SD)

Characteristics	Radiofrequency device ($n = 31$)	Control ($n = 32$)	P value
Age (years)	24.13 ± 3.92	22.72 ± 2.74	0.18
Sex (M:F no. (%))	20:11 (65:35%)	22:10 (69:31%)	0.72
Height (cm)	171.75 ± 9.16	171.08 ± 8.95	0.77
Weight (kg)	63.98 ± 11.62	67.10 ± 12.66	0.27
Acne lesion count at baseline	46.35 ± 30.50	34.25 ± 21.42	0.07
IGA score at baseline	4.42 ± 0.50	4.27 ± 0.45	0.20

IGA, Investigator's Global Assessment.

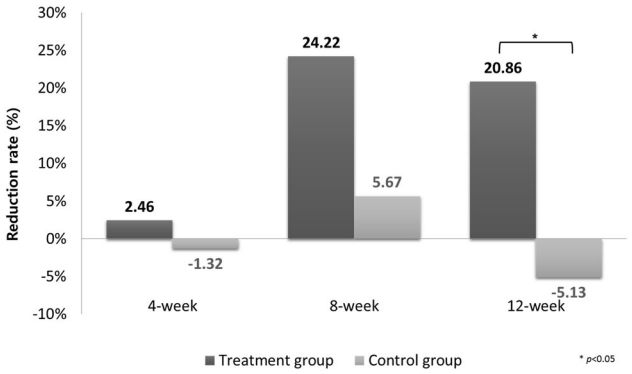

Fig. 2. Reduction rate in acne lesion count evaluated by two independent investigators for 4, 8, and 12 weeks.

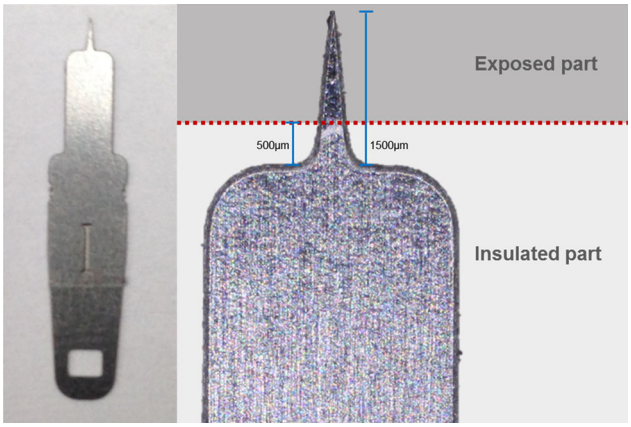

Fig. 4. Magnified image of a disposable microneedle with a T-shaped insulated shoulder (I-type microneedle).

device in acne patients that lasted for an extended period with decreased recurrence rate. Considering these results, it is possible that an extension of the study period would lead to better outcomes. Second, the effect of needling, the method used in the control group, was higher than expected. Treatment effectiveness of the RF device may, therefore, have been underestimated. The effectiveness of needling alone would partially explain the finding that little difference in treatment satisfaction was found between the groups. Third, there is a discrepancy in the result of "the mean reduction rate" and "the decrement in the mean acne count," especially in the control group at 12 weeks; the reduction rate has negative quantity ($-5.13 \pm 75.21\%$) while the decrement acne count was positive quantity (3.17 ± 23.80). Considerable variations in the baseline acne counts and treatment responses between patients seem to contribute to the discrepancy.

Previously, various reports indicated that RF reduces excretion of sebum through destruction of the sebaceous glands [11–13]. Kobayashi [11] also showed that fewer sebaceous glands and the formation of fibrosis were observed after selective sebaceous gland electrothermolysis in a preliminary histological study. Destroyed sebaceous glands may be replaced by the fibrous tissue. The treatment may also result in pore size reduction [19] with skin tightening [20,21]. Altogether, results from these studies suggest that this technique may represent a new therapeutic modality in the treatment of acne.

There are possible concerns about the immunity/host defense issue that may arise from the destruction of all of the sebaceous gland because recent evidences have indicated that human sebaceous glands contribute to skin immune defense by releasing antimicrobial peptides [22]. However, the present treatment modality is relatively free from such concerns as it targets and destructs the active and recurrent acne spots exclusively rather than the every pilocebaceous units on the face. Moreover, the treatment options that results in non-selective reduction of the sebaceous gland activity on the whole face (i.e., PDT, isotretinoin) are not related with such issue [22,23].

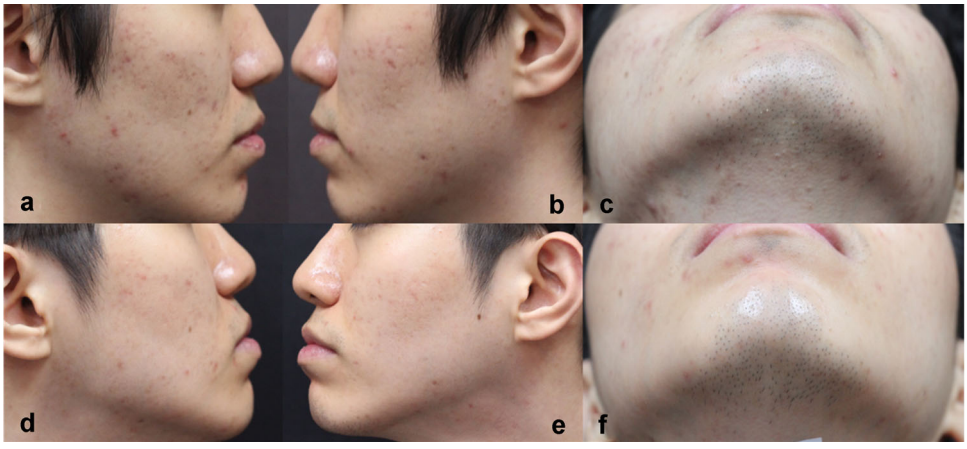

Fig. 3. A representative case of a patient from the radiofrequency device-treated group. Facial acne in a 23-year-old man before the initiation of treatment (a) right, (b) left, (c) inferior, 4 weeks after three serial treatments (12-week follow-up) (d) right, (e) left, (f) inferior.

CONCLUSION

This study is the first randomized clinical trial using a single microneedle RF device for the treatment of moderate-to-severe acne. Results clearly show that a single microneedle device is capable of improving the facial inflammatory acne. As with previous pilot studies, the technique proved that a RF device is an effective and safe modality for the treatment of acne in a large population. However, due to the short duration of the study, an extended study is still required to evaluate the long-term effects of this promising new technique.

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