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Research Article

Intradermal Local Injection of Autologous Cell-Free Fat Extract for the Treatment of Refractory Postinflammatory Hyperpigmentation

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Current treatment modalities for postinflammatory hyperpigmentation (PIH) often fall short in delivering satisfactory results for some patients. Therefore, this study aimed to assess the efficacy and tolerability of autologous cell-free fat extract (CEFFE) in the treatment of PIH. We enrolled 15 patients with PIH and administered them with five intracutaneous CEFFE injections, each at a two-week interval. Evaluation included efficacy assessment using objective (standard two-dimensional photos, VISIA®-photos, brown spot (BS) index, lesion lightness, lesion color, and trans-epidermal water loss) and subjective (Global Aesthetic Improvement Scale and Likert satisfaction scale) parameters and tolerance assessment. Following CEFFE treatment, significant reductions were observed in the BS index ($p < 0.05$) and transepidermal water loss ($p < 0.05$), while skin lightness and lesion color showed significant improvements ($p < 0.05$) at the 12-month follow-up. Subjectively, 93.33% of patients reported improved or greatly improved conditions after 12 months of treatment. Transient local bruising and stinging were the only observed treatment-related adverse events, with no serious complications reported. These findings demonstrate that intradermal injections of CEFFE are well-tolerated and effective for the treatment of PIH. This trial is registered with ChiCTR2000039381.

1. Introduction

Postinflammatory hyperpigmentation (PIH) is a common dermatological condition characterized by long-term hyperpigmentation, skin barrier damage, and atrophic scarring [1]. It is often a consequence of inflammatory processes, resulting in a complex pathogenesis that poses challenges for conventional treatment approaches. PIH lesions, frequently observed on the face with a considerable size, cause emotional distress and have a profound impact on the quality of life of affected individuals [2, 3]. Unfortunately, existing therapies for PIH, including hypo-pigmenting agents, chemical peels, and laser treatments, often fail to achieve satisfactory outcomes, necessitating a prolonged treatment duration [4–6]. Consequently, an urgent need exists to develop a comprehensive therapy that effectively addresses PIH while ensuring tolerability.

Cell-free fat extract (CEFFE) is an intriguing treatment option derived from adipose tissue through emulsification and centrifugation [7]. It contains high concentrations of diverse soluble active proteins, including transforming growth factor (TGF)-β1, TGF-β2, interleukin (IL)-4, and vascular endothelial growth factor (VEGF), which play pivotal roles in healing and regenerative processes [2, 8]. Extensive research has already demonstrated the therapeutic efficacy of CEFFE in various dermatological diseases, including photo-aging, flap grafting, and the treatment of refractory wounds [9–11]. Moreover, our unpublished

findings have confirmed its potential in ameliorating hyperpigmentation, as evidenced by positive outcomes in a zebrafish model.

Given the regenerative properties of CEFFE and its promising track record in dermatological conditions, we hypothesize that CEFFE therapy holds considerable promise as an effective and well-tolerated treatment modality for postinflammatory hyperpigmentation. Consequently, this study aims to evaluate the efficacy and tolerability of CEFFE therapy in patients with PIH. We aspire to contribute to the development of an innovative and comprehensive therapeutic approach that addresses the unmet medical needs of individuals with PIH by investigating the effects of CEFFE on hyperpigmentation.

2. Materials and Methods

2.1. Subjects and Inclusion and Exclusion Criteria. This study was approved by the Institutional Review and Ethics Board of Shanghai Ninth People's Hospital, Shanghai Jiao Tong University School of Medicine (SH9H-2020-T97-3) and registered at https://www.chictr.org.cn (ChiCTR2000039381). Fifteen patients were enrolled in this study between October 2020 and October 2021 and have provided written informed consent. The patients were women aged 18–33 years, with post-radiotherapy pigmentation, in which conventional approaches, such as topical medications or laser therapies, were ineffective. A single group, repeated measures design was used for this study.

The exclusion criteria were the following: current or planned pregnancy; the presence of a wound or broken epidermis in the focus area; serious underlying diseases, including mental disorders; known hypersensitivity to lidocaine; body mass index (BMI) <18 or >30 kg/m^2; therapy, such as laser, mesotherapy, and chemical peeling within the last 6 months before this study; or enrollment in other clinical trials.

2.2. CEFFE Preparation and Treatment. Liposuction was performed using a standard cannula (3 mm) with large side holes (2 × 7 mm) after local infiltration injections with modified Klein solution. Approximately 100 mL of fat was collected from each patient. Fat tissues were washed with saline solution to remove remnant blood cells and centrifuged at 1,200 × g for 3 min. The middle fat layer was collected for further emulsification through two syringes connected by a 2 mm diameter Luer lock connector (B. Braun Medical Inc., Melsungen, Germany) and shuffled 60 times. The emulsified fat was then centrifuged at 1,200 × g for 5 min and separated into four layers (oil, fat, CEFFE, and cell fragment pellet). CEFFE was collected and filtered through a 0.22 μm filter (Corning Glass Works, Corning, NY, USA) and stored at −80°C in a 1.8 mL sterilized cryopreservation tube (Thermo Fisher Scientific, Waltham, MA, USA). Approximately 10 mL of CEFFE was obtained from each patient (Supplementary Video File (available here)).

The time points of patients receiving treatment and follow-up after enrollment are shown in Figure 1(a). The relevant treatment frequencies refer to the platelet-rich plasma treatment for hyper-pigmentation containing melasma, acne scar, and periocular hyperpigmentation [12–15]. Each patient received five intracutaneous CEFFE injections at the lesion site with a two-week interval. The first injection was performed two weeks after CEFFE preparation. After the final injection, the patients underwent three follow-ups at 3, 6, and 12 months posttreatment.

One hour before every injection, the pigmented area was cleaned and topical anesthetic ointment comprising 25% lidocaine and 25% procaine (Ziguang, Beijing, China) was applied. After sterilization, CEFFE was intradermal injected by the nappage technique using a 32-G needle (0.1 mL per point in a linear pattern and the typical total treatment course involves injecting a volume of 8–10 mL; injection points were 1 cm apart; Figure 1(b)).

2.3. Objective Efficacy Assessment. Standard two-dimensional (2D) photographs and quantitative analysis of brown spots (BS) were conducted using VISIA-CR® (Canfield Scientific, Fairfield, NJ, USA) before treatment and at every follow-up visit (3, 6, and 12 months after the final treatment). Measurements were performed at fixed locations for each patient and follow-up.

Lesion color was measured by tristimulus colorimetric using a skin colorimeter CL400 probe (Courage–Khazaka, Germany) [16]. The three darkest areas of the lesion were tested for each patient. L^* value indicates lightness, is correlated with the level of pigmentation of the skin, and is represented on a vertical axis with values from 0 (black) to 100 (white). a^* and b^* are chromaticity coordinates. The a^* value indicates the red-green component of a color and is correlated with erythema. The b^* value indicates the blue-yellow component and is correlated with pigmentation and tanning. The change in lightness was calculated as follows:

$$\Delta L^*\% = \frac{L^* t}{L^* \text{baseline}} \times 100\%, \tag{1}$$

where L^* baseline represents the baseline lightness (before CEFFE treatment) and L^*t represents the skin lightness at 3, 6, or 12 months after the final treatment ($t = 3$, 6, or 12).

The change in skin color is calculated as follows:

$$\Delta E^*_{ab} = \sqrt{\left(L^* \text{t} - L^* \text{baseline}\right)^2 + \left(\text{t} - a^* \text{baseline}\right)^2 + \left(b^* \text{t} - b^* \text{baseline}\right)^2}. \tag{2}$$

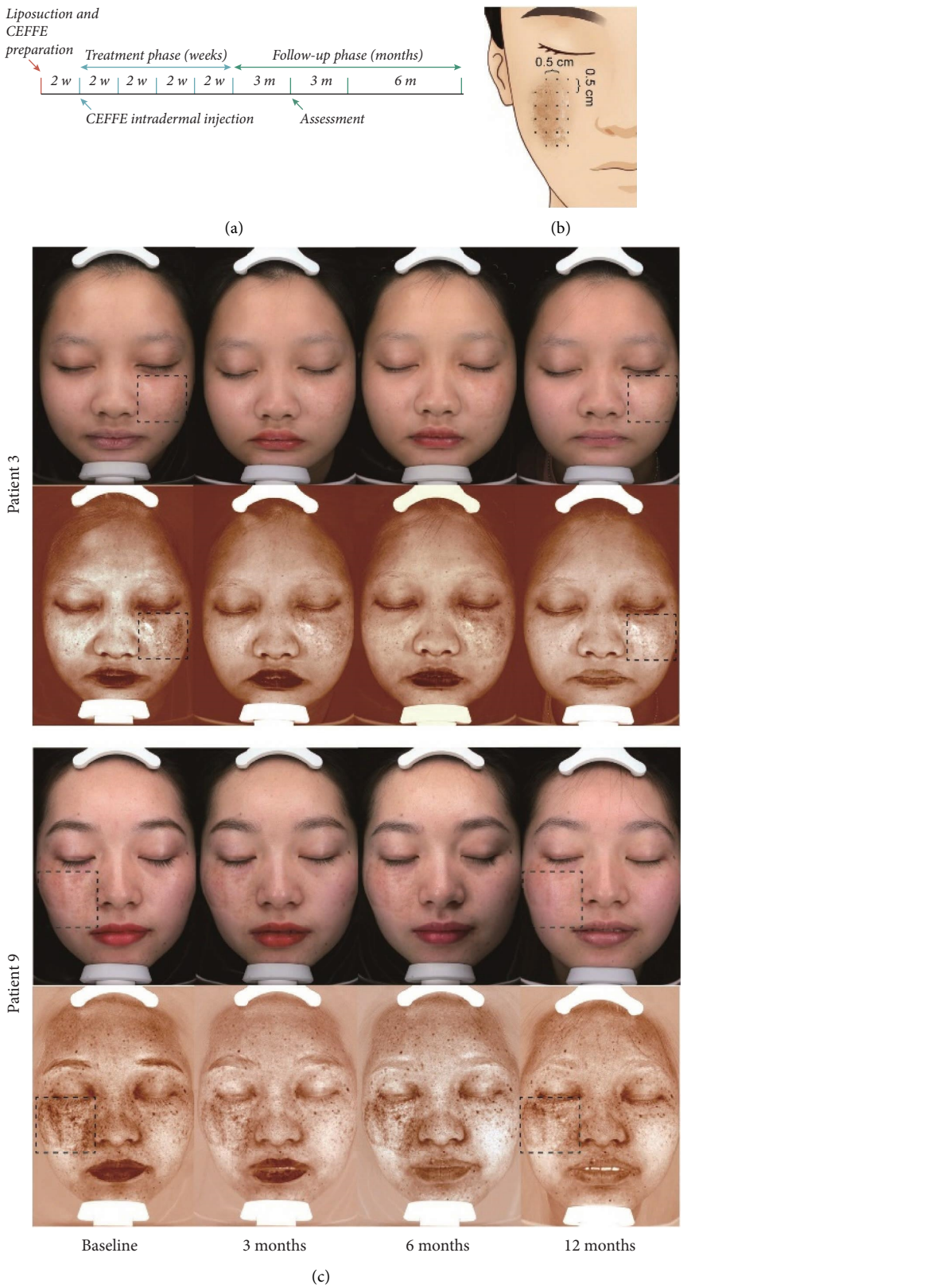

FIGURE 1: (a) Treatment flow chart. (b) Schematic diagram of injection position. (c) Standard two-dimensional photos and VISIA-photos for patient 3 (female, 21 years old) and patient 9 (female, 26 years old) on the baseline, 3 months', 6 months', and 12 months' follow-up. Black dashed box indicated the hyperpigmentation area.

Transepidermal water loss (TEWL) was measured using a Tewameter® TM300 and used to estimate the skin barrier function [17]. Measurements were taken at fixed locations for each follow-up visit. The change in skin barrier function was calculated as follows:

$$\text{TEWL\%} = \frac{\text{TEWL}^{*}t}{\text{TEWL}^{*}\text{baseline}} \times 100\% \, (t = 3, 6, 12). \quad (3)$$

2.4. Subjective Efficacy Assessment. Global aesthetic improvement in appearance during each follow-up compared to pretreatment was assessed using the Global Aesthetic Improvement Scale (GAIS) [18]. GAIS scores range from −2 (much worse) to 2 (very much improved). The satisfaction of patients at 12 months after the final treatment was assessed using the Likert Satisfaction Scale (LSS) [19]. LSS measures specific items utilizing a five-point scale: very dissatisfied, dissatisfied, slightly satisfied, satisfied, or very satisfied.

2.5. Tolerance Assessments. The tolerance of each treatment was evaluated based on the number of injection-related events (IREs) reported by the subjects [20]. During the first 14 days after injection, local tolerability was assessed by the frequency and severity of predefined IREs.

2.6. Statistical Analysis. The nonparametric Friedman test was used to compare the outcome measures at the four assessment times (baseline, 3, 6, and 12 months after the final treatment). Statistical analysis and graphical work were performed using *R* (*R* Foundation for Statistical Computing, Vienna, Austria). "*tidyverse*," "*ggplot,*" and "ggsci" packages were used to visualize the results. Continuous variables are presented as the median (first quartile; third quartile) or mean ± standard deviation. Statistical significance was set at $p < 0.05$.

3. Results

The mean ± SD age of the participants at the baseline was 22.13 ± 4.29 years (range from 18 to 33). Hyperpigmentation developed on the face and resulted following strontium^{90} radiotherapy administered for the treatment of IH. The average duration of hyperpigmentation was 18.4 years, and its average area was 8.27 ± 8.15 cm^2. All patients have received multiple medications including laser therapy (3–12 times) before CEFFE treatment with limited effects. The height, weight, and body mass index (BMI) of the patients was 164.30 ± 3.58 cm, 55.57 ± 4.70 kg, and 20.56 ± 1.55 kg/m^2, respectively (Table 1).

3.1. Objective Efficacy Assessments. Representative two-dimensional (2D) and VISIA® images from the baseline to the third follow-up of two participants (patients three and nine) treated with CEFFE are shown in Figure 1(c). At the end of the 12-month follow-up period, the area of irregularly pigmented lesions decreased and lightness improved, compared with those at the baseline. The brown spot index (Figure 2(a)) showed a downward trend as time passed (94.87% [91.60%; 99.56%]; 95.26% [90.38%; 96.16%]; 54.01% [43.89%; 77.35%]), with the most pronounced decrease being at the end of the 12-month follow-up period compared to that at the baseline ($p < 0.05$). Skin lightness (Figure 2(b)) improved significantly to different extents during the follow-up period (109.42% [103.87%; 121.02%], $p < 0.05$; 109.73% [105.45%; 130.58%]; 118.22% [109.06%; 129.29%], $p < 0.05$), and the largest improvement was observed at the end of the 12-month follow-up period, as demonstrated by the ΔE_{ab} values (Figure 2(c); 2.78 [1.05; 5.40]; 3.37 [1.57; 5.27]; 3.27 [1.87; 5.98]). TEWL (Figure 2(d)) was 70.37% (47.73%; 85.86%), 67.83% (62.35%; 90.48%), and 65.86% (48.24%; 78.23%) 3, 6, and 12 months posttreatment, respectively. The improvement in the skin barrier function was most evident at the end of the 12-month follow-up period compared to that at the baseline ($p < 0.05$).

3.2. Subjective Efficacy Assessment. According to the Global Aesthetic Improvement Scale (Figure 3), 93.33% ($n = 14$) of the patients showed "improved" or "very much improved" conditions 12 months after treatment. Based on the Likert satisfaction scale Table 2), 100% ($n = 15$) of the patients were either satisfied or very satisfied with the CEFFE treatment.

3.3. Tolerance Assessments. CEFFE treatment was well tolerated; treatment-related adverse events including contacting bruise, and stinging were transient, of mild-to-moderate severity, and localized at the injection sites. All patients experienced transient and tolerable stinging during injection, and 53.33% of the patients ($n = 8$) showed mild bruises after injection, which recovered within 4.13 ± 3.08 days (Table 3). There were no dropouts or withdrawals due to IREs in this study. To date, no serious IREs have been reported.

4. Discussion

PIH significantly impacts the quality of life of patients and satisfaction with their appearance [2]. Unfortunately, current therapeutic options for PIH often fall short of meeting expectations of patients [1]. In this study, we investigated the efficacy and tolerability of CEFFE as a potential treatment for PIH.

Our objective evaluation revealed that CEFFE treatment led to significant improvements in the general appearance and lightness of the skin, indicating its effectiveness in reducing pigmentation. These positive outcomes can be attributed to various factors. VEGF has been reported to inhibit tyrosinase activity, while IL-4 suppresses melanocyte formation through the JAK2-STAT6 pathway [1, 21]. Furthermore, CEFFE possesses antioxidant, antiapoptotic, and proangiogenic properties, as observed in our previous studies [7, 11, 22]. These properties contribute to the protection of dermal fibroblasts and skin from UVB-induced photoaging [23]. CEFFE treatment also improved skin texture and enhanced barrier function, which can be attributed to the stimulation of neovascularization by VEGF,

Table 1: Clinical characteristics of all 15 patients.

Patient no.	Sex	Age (years)	Height (cm)	Weight (kg)	BMI (kg/m^2)	Length × width (cm)	Laser treatments (times)
1	F	24	163	59.5	22.39	2.2 × 1.8	6
2	F	25	162	58	22.10	1.7 × 1.3	5
3	F	21	168	54	19.13	3.0 × 1.4	4
4	F	24	166	52	18.87	1.8 × 2.1	5
5	F	21	165	51	18.73	2.6 × 2.3	3
6	F	19	165	60	22.03	4.1 × 4.5	12
7	F	18	165	54	19.83	1.8 × 2.2	6
8	F	24	163	57	21.45	3.8 × 5.0	5
9	F	26	165	60	22.03	2.1 × 1.3	3
10	F	18	160	45	17.57	1.5 × 1.6	5
11	F	25	161	50	19.28	2.4 × 2.2	7
12	F	33	159	54	21.35	3.7 × 4.1	8
13	F	18	164	57	21.19	2.1 × 2.7	3
14	M	18	174	62	20.47	6.9 × 4.2	11
15	F	18	164	60	22.04	1.7 × 1.3	3

F, female; M, male.

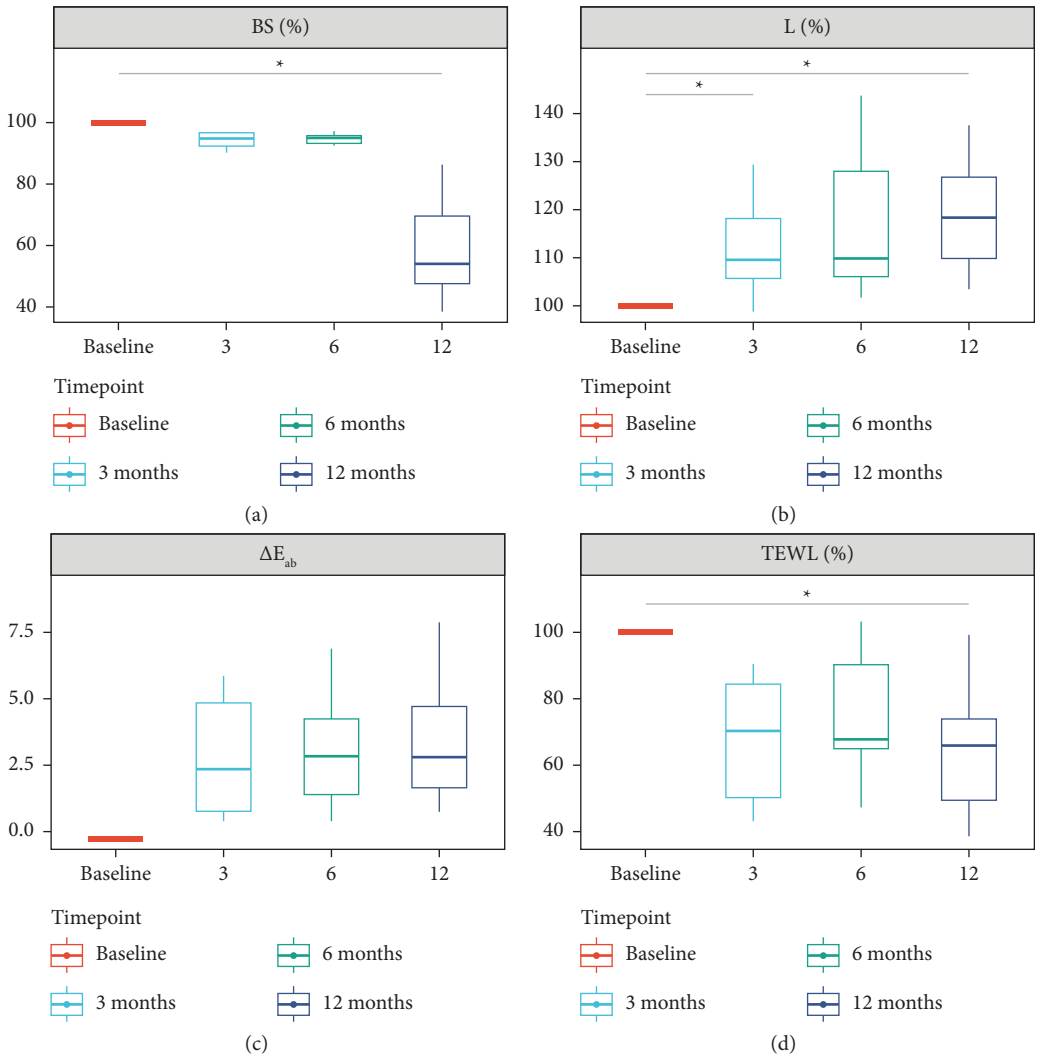

Figure 2: The change of objective assessments from the baseline to 12 months' follow-up. (a) Brown spot index. (b) Lesion lightness. (c) Lesion color. (d) Transepidermal water loss.

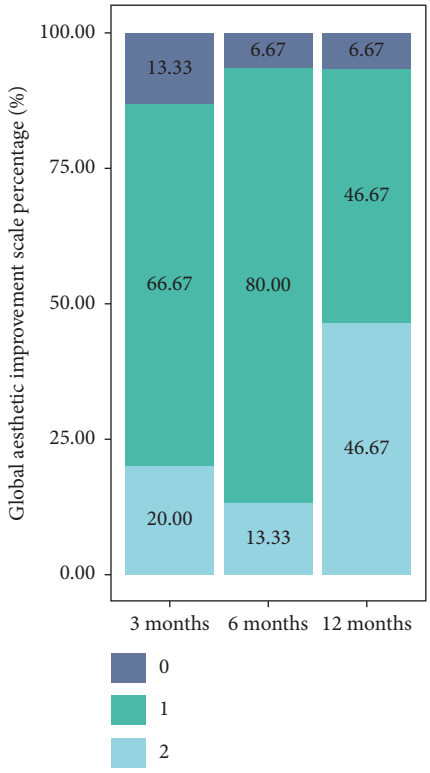

Figure 3: Global aesthetic improvement scale percentage at 3 months', 6 months', and 12 months' follow-up.

Table 2: Likert satisfaction scale results.

Degree of the satisfaction scale	Number (%)
Very dissatisfied	0 (0.00%)
Dissatisfied	0 (0.00%)
Slightly satisfied	0 (0.000%)
Satisfied	11 (73.33%)
Very satisfied	4 (26.67%)

Table 3: Tolerability assessments results.

Parameter	Number (%)	During (mean ± SD, days)
Bruise	8 (53.33%)	4.13 ± 3.08
Erythema	0 (0.00%)	0
Edema	0 (0.00%)	0
Burning	0 (0.00%)	0
Stinging	15 (100.00%)	0.0034 ± 0.0014
Itching	0 (0.00%)	0

epidermal cell proliferation by a basic fibroblast growth factor, and fibroblast proliferation by an epidermal growth factor. Notably, the sustained reduction in skin lesions observed 12 months after CEFFE treatment suggests potential changes in the skin lesion microenvironment.

Subjective evaluation by patients reporting a substantial decrease in the overall intensity of dark spots further supported the efficacy of CEFFE treatment. Tolerance to CEFFE was favorable, with only transient bruises observed post-injection, and no other patients reported adverse skin reactions. Consistent with our previous studies, CEFFE administration did not elicit immunogenicity, cytotoxicity, intradermal reactions, or acute systemic toxicity [24].

Additionally, CEFFE preparation is convenient and can be utilized for multiple treatments, suggesting its potential applicability in other refractory hyperpigmentation disorders, such as melasma, acne scars, and periocular hyperpigmentation. However, it is important to acknowledge the limitations of our study, including the small sample size and the complexity of determining the specific factors within CEFFE that contribute to its efficacy.

In summary, our study demonstrates that CEFFE is a well-tolerated agent that effectively reduces PIH. The objective and subjective improvements observed support its potential as a promising therapeutic option for patients with postradiotherapy PIH. Further research with larger sample sizes is necessary to validate these findings and gain a deeper understanding of the underlying mechanisms.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Consent

The patients in this manuscript have given written informed consent to publication of their case details.

Disclosure

The funder had no role in data collection, management, analysis, publication decision, or manuscript preparation.

Conflicts of Interest

The authors declare no conflicts of interest.

Authors' Contributions

The study was designed by WL and WZ. YC and GJ contributed to experimentation, data collection, and data analyses. ZJ contributed to manuscript writing, editing, and data visualization. BK and HZ contributed to manuscript reviewing. All authors read and approved the final manuscript. Yizuo Cai and Zhuoxuan Jia contributed equally to this work.

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Supplementary Materials

Supplementary video: preparation of CEFFE in the operating room after liposuction. (*Supplementary Materials*)

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