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Effect of ultrasound-guided epidermal growth factor injection combined with carbon dioxide laser on treatment of facial acne scars

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ABSTRACT

Background: To determine the therapeutic effect of ultrasound-guided epidermal growth factor (EGF) injection combined with carbon dioxide laser on facial acne scars. ***Materials and Methods:*** One hundred patients with facial acne scars admitted to the dermatology department from October 2021 to October 2022 were selected as the subjects of this study. The observation group (OG) received ultrasound guided EGF injection combined with carbon dioxide 2 (CO_2) laser treatment, and the control group (CG) received CO_2 laser treatment alone. The clinical outcomes and the recovery time after treatment were recorded for both groups of patients. Quantitative skin analysis including skin spots, red mass, pores and wrinkles were performed before and after treatment by VISIA skin detector, and inflammatory factors levels were measured. ***Results:*** The pain duration, erythema duration, incrustation time, decrustation time and incidence of adverse reactions in the OG were lower than those in the CG, while the total efficiency of treatment was higher than that in the CG ($P<0.05$). In addition, the results of quantitative analysis of skin spots, red matter, pores and wrinkles were higher in the OG and inflammatory factors levels were lower in the CG after treatment ($P<0.05$). ***Conclusion:*** EGF combined with CO_2 laser can effectively improve scarring symptoms and shorten the recovery period in patients with facial acne scars.

INTRODUCTION

Acne lesions are usually found on the cheeks, forehead and jaw, but may also involve the trunk and other parts of the body [1]. Acne occurs in young men and women between the ages of 15 and 25. Once acne is squeezed by external forces, it can easily cause local skin damage, and weakened skin barrier protection can lead to sebaceous gland inflammation, and the inflammation can aggravate skin tissue destruction and lead to scar formation, seriously affecting facial aesthetics and causing serious psychological burden to adolescent patients [2].

The common clinical treatment methods are skin grinding and excision, which [3]. The ultra-pulsed carbon dioxide 2 (CO_2) laser is often used to treat scarring, freckles and other common clinical dermatological conditions, which not only can repair beautifully damaged skin, but also has a high precision with a vaporization depth of only 0.01 mm [4]. By dividing the fractional laser into multiple laser beams and optimizing the penetration depth of the laser, the skin collagen and elastic fiber proliferation and remodeling are obtained through rapid crawling of activated keratin-forming cells at the edge of the injury area, which promotes the rearrangement of dermal tissue and stimulates the regeneration of local collagen and elastic fiber proteins, producing a focal photothermal effect to modify the depressed scar tissue structure [5]. At the same time, the CO_2 laser can and continues to soften scar tissue, allowing skin elasticity to be restored [6]. During the treatment, the laser absorbs the base group is water in the skin, which constantly shrinks the collagen fibers in the dermis, leading to their denaturation, accelerates the healing of wounds in the dermis, and promotes the deposition of skin collagen as well as its proliferation, with the advantages of short treatment time, fast healing, no bleeding, and no pain [7]. However, with the long-term application of ultra-pulsed CO_2 laser treatment, researchers have found that some patients still experience scarring, changes in skin color and texture, and some patients develop infections, with a higher risk of adverse effects in those with scar constitution [8, 9]. Therefore, it is of positive significance to actively explore other adjuvant methods for the treatment of acne scars.

Epidermal growth factor (EGF) can promote skin growth [10]. While the introduction of EGF by ultrasound can effectively promote cell proliferation

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and increase skin tissue repair, while regulating the synthesis of related proteins, which has a positive effect on promoting scar repair [11]. Some of the published studies are older and some are cohort analyses with small sample sizes, which may lead to less credible results. To address these limitations, we accumulated a sufficient number of cases and conducted a clinical randomized controlled trial, which could provide a more reliable reference and guidance for the current clinical application of EGF combined with CO_2 laser.

MATERIALS AND METHODS

Patients

One hundred patients with facial acne scars admitted to the dermatology department of The Affiliated Suzhou Hospital of Nanjing Medical University from October 2021 to October 2022 were selected as the subjects of this study. This study met the requirements of the Medical Ethics Committee and was reviewed and approved by The Affiliated Suzhou Hospital of Nanjing Medical University (No. EL2021025, October 2021). These patients were divided into two groups, with 50 patients in each group. The observation group (OG) received ultrasound guided EGF injection combined with CO_2 laser treatment, and the control group (CG) received CO_2 laser treatment alone.

Inclusion and exclusion criteria

Inclusion criteria: Patients all met the diagnostic criteria for facial acne scars [12] and had consistent clinical symptoms; no recent use of antibacterial and hormonal drugs; complete clinical data. Exclusion criteria: coagulation disorders; mental, speech and hearing impairments; drug allergies; combination of other major diseases; pregnant and lactating women; patients who cannot be followed up as scheduled or whose treatment was interrupted in the middle of the visit for various reasons.

Methods

Control group (CG): The patient's face was routinely cleaned, supine on the treatment bed, and the face was applied with compound lidocaine ointment (Tongfang Pharmaceutical Group Limited, H20063466, China) for local anesthesia and covered with plastic wrap, and the ointment was removed after waiting for 30-60 min. After disinfection, treatment was performed with a fractional CO_2 laser (Wuhan/Jinxingu Technology, JLT-100B, China) with a wavelength setting of 10600 nm, an energy range of 60-80 mJ/cm^2, and a fractional coverage setting of 0.72%-2.89%. The treatment was repeated once, and the patient's scar was scanned according to the shape of the scar. After the laser treatment, local ice pack is applied cold, 1 time/month, 3 times as a course of treatment. OG: On the basis of the CG combined with ultrasound-guided injection of EGF, patients were treated with sterilized cold compresses after the end of laser treatment, followed by taking appropriate amount of EGF gel (Guilin Warnover Gene Pharmaceutical Co., Ltd., S20020112, China) and applying it on the affected area, and using ZP-A8 ultrasonic drug introduction instrument (Maithong, ZP-A8, China) for drug introduction with an intensity of 1.25 W/cm^2 and an introduction time of 15 min. Patients in both groups continued treatment for two courses.

Outcome measures

The duration of pain and erythema, and time of incrustation and decrustation after treatment were recorded. And quantitative skin analysis before and after the treatment, including skin spots, red mass, pores and wrinkles, were detected and analyzed using VISIA skin detector [Coolin (Shanghai) Trading Co., China], the lower the score indicates the worse effect. The severity of the patients' facial acne scar was assessed by following the Echelle d'Evaluation Clinique des Cicatrices d'Acne (ECCA) Score [13] and the Vancouver Scar Scale (VSS) [14], respectively, with higher scores indicating more severe scarring. Fasting venous blood was collected from patients, and interleukin-2 (IL-2) and interleukin-6 (IL-6) levels were measured by enzyme linked immunosorbent assay (ELISA) in two groups of patients, and the kits were purchased from Wuhan Elite Biotechnology Co. (China). Patient outcomes were assessed with reference to acne scar treatment guidelines [15]. Cured: bright and shiny skin, no unevenness or pain or itching, no recurrence. Markedly effective: The symptoms are significantly improved, and the color and flatness of most of the lesion area is close to the surrounding normal skin. Effective: The symptoms have improved and about half of the lesion area is in the recovery stage. Ineffective: no significant improvement in symptoms. Finally, the adverse reactions during the treatment were counted in both groups.

Statistical methods

SPSS25.0 statistical software (IBM, United States) was used to statistically analyze the data results. The counting data were expressed as (%) and compared by chi-square test. While the measurement data were expressed as (`c±s) and the t-test was used for comparison between groups, and the paired t-test was used for that before and after treatment. P<0.05 considered the difference to be statistically significant.

RESULTS

Baseline data for both groups

The data of age, gender, and scar site were collected from the two groups. The statistical analysis

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showed that the general data of the two groups were not statistically different (P>0.05) (table 1).

Table 1. There was no statistically significant difference between the baseline data of the two groups. Body Mass Index (BMI).

Group	n	Age	Duration of illness (months)	BMI (kg/ m^2)	Scar site Forehead / Isthmus / Temporal / Mixed			
Observation	50	20.6±2.3	15.6±3.1	18.5±2.5	11 (22.0)	17 (34.0)	9 (18.0)	13 (26.0)
Control	50	21.1±2.6	15.5±3.4	18.7±2.9	10 (20.0)	19 (38.0)	10 (20.0)	11 (22.0)
χ^2/t		1.019	0.154	0.369	0.378			
P		0.311	0.878	0.713	0.945			

Comparison of clinical indicators between both groups

After comparing the duration of pain and erythema, and time of incrustation and decrustation in the two groups, we found that the time spent in the OG was significantly shorter than that in the CG (P<0.05). It showed that the improvement of clinical symptoms in the OG was better than that in the CG (figure 1).

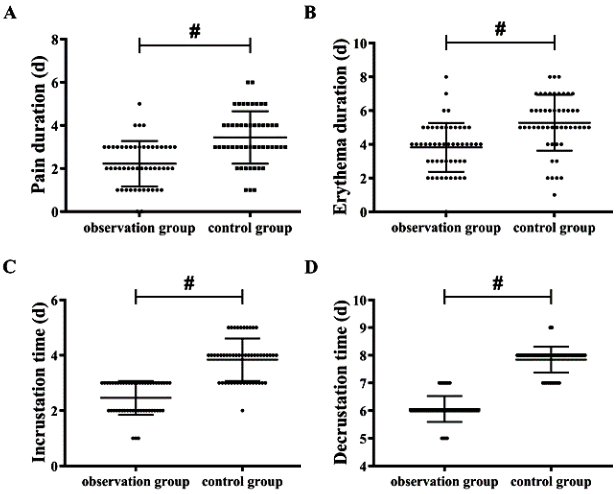

Figure 1. Comparison of clinical indicators between both groups, both the duration of pain and erythema, and time of incrustation and decrustation were shorter in the OG shorter than in the CG. **A)** Pain duration. **B)** Erythema duration. **C)** Incrustation time. **D)** Decrustation time. #P<0.05.

Clinical efficacy of both groups

The total effective rate was 96% in the OG and 84% in the CG. There was a difference between the total effective rate of the two groups (P<0.05), and the efficacy of the OG was better than that of the CG (table 2).

Table 2. Clinical efficacy of both groups.

Group	n	Cured	Markedly effective	Effective	Ineffective	Effective rate
Observation	50	23 (46.0%)	16 (32.0%)	9 (18.0%)	2(4.0%)	48 (96.0%)
Control	50	16 (32.0%)	14 (28.0%)	12 (24.0%)	8(16.0%)	42 (84.0%)
χ^2						4.000
P						0.046

Quantitative skin analysis results for both groups

Pre-treatment analysis showed no statistically significant differences in the quantitative comparison of skin spots, red mass, pores and wrinkles between the two groups (P>0.05). While after treatment, both groups improved their skin problems and the quantitative analysis was higher than before treatment (P<0.05). In the OG, all quantitative results were higher than those in the CG (P<0.05), and the improvement was more significant (figure 2).

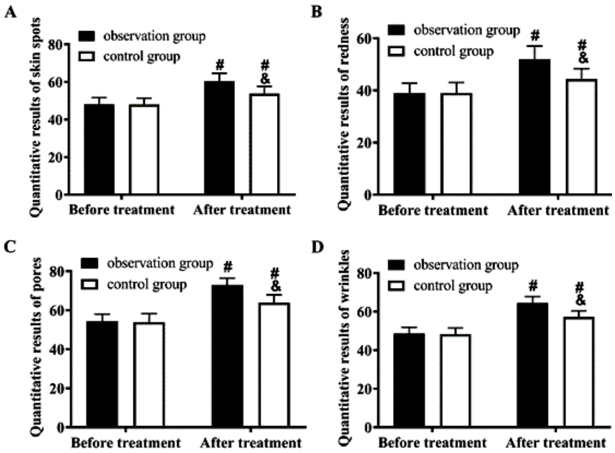

Figure 2. Quantitative skin analysis results for both groups, The quantitative results of skin spots, red mass, pores and wrinkles were higher in both groups after treatment, and the OG was higher than the CG. **A)** Quantitative results of skin spots. **B)** Quantitative results of redness. **C)** Quantitative results of pores. **D)** Quantitative results of wrinkles. Compared with before treatment #P<0.05, compared with the CG & P<0.05.

ECCA and VSS scores for both groups

Before treatment, ECCA and VSS were similarly not significantly different between the two groups (P>0.05). While after treatment, ECCA and VSS were lower in both groups than before treatment (P<0.05), and ECCA and VSS in the OG were lower than those in the CG (P<0.05) (figure 3).

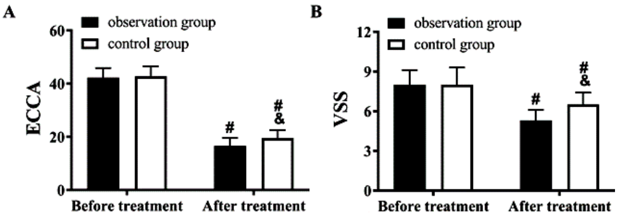

Figure 3. ECCA and VSS scores for both groups, the ECCA and VSS decreased in both groups after treatment, and were lower in the OG than in the CG. A) Echelle d'Evaluation Clinique des Cicatrices d'Acne (ECCA) Score. B) Vancouver Scar Scale (VSS). Compared with before treatment #P<0.05, compared with the CG & P<0.05.

Levels of inflammatory factors in both groups

The results of inflammatory factors manifested that the levels of IL-2 and IL-6 did not differ between the two groups before treatment (P>0.05), while the levels of IL-2 and IL-6 decreased in both groups after treatment compared with those before treatment

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(P<0.05), and the levels of inflammatory factors in the OG were lower than those in the CG (P<0.05) (figure 4).

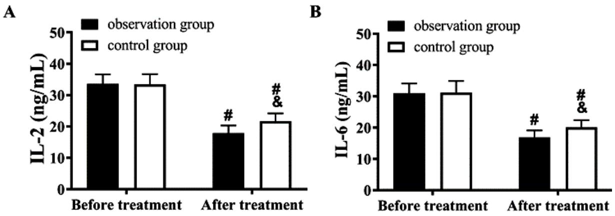

Figure 4. Levels of inflammatory factors in both groups, both IL-2 and IL-6 were reduced after treatment in both groups and were lower in the OG than in the CG. **A)** interleukin-2 (IL-2). **B)** interleukin-6 (IL-6). Compared with before treatment #P<0.05, compared with the CG & P<0.05.

Incidence of adverse reactions in both groups

The overall incidence of adverse reactions was 4% in the OG and 18% in the CG. It was seen that the incidence of adverse reactions in the OG was lower than that in the CG (P<0.05) (table 3).

Table 3. Incidence of adverse reactions in both groups, the OG was even lower than the CG.

Group	n	Hyperpig-mentation	Infection	Edema	Constant blushing	Total incidence
Observation	50	1(2.0%)	0(0%)	0(0%)	1(2.0%)	2(4.0%)
Control	50	3(6.0%)	1(2.0%)	2(4.0%)	3(6.0%)	9(18.0%)
χ^2						5.005
P						0.025*

DISCUSSION

Facial acne is a common chronic inflammatory follicular sebaceous gland disease that is highly susceptible to depressed acne in severe cases and has a serious impact on the psychological health of patients [(4)]. The main cause of depressed scar acne is the incongruent ratio of matrix metalloproteinases, inhibitors, resulting in reduced and uneven collagen deposition, etc. [(16)]. Facial acne depressed scarring can cause the facial skin to lose its original luster and affect patients' facial aesthetics, making it a major challenge for clinical treatment [(17)].

In this study, patients treated by EGF combined with CO_2 laser showed more significant improvement in skin blemishes, redness, pores and wrinkle scores, and better clinical outcomes, suggesting that we have a superior therapeutic effect of EGF combined with CO_2 laser on facial acne scars, similar to the results of previous studies [(18)]. Patients' duration of pain and erythema, and time of incrustation and decrustation were all significantly reduced, which further indicated that EGF combined with CO_2 laser could more effectively promote patients' recovery cycle and had higher clinical application value. And for this reason, we speculate that it may be related to the modulatory effect of EGF on the inflammation.

It is well known that the occurrence of acne is also a reflection of the inflammation of the organism, which is mainly caused by the interaction of the metabolism of the acne short bacillus vaccine and the immune response of the organism [(19)]. The massive release of inflammatory factors, such as IL-2 and IL- 6, enhances the phagocytosis of neutrophils and is involved in the intrinsic immune response of the body, promoting the production of other cytokines and aggravating the inflammation in acne [(20)]. Also, inflammatory factors increase the proliferation and maturation of non-monocyte-dependent T cells, which constantly stimulate the proliferation of antigen-specific B cells and induce the pathological process of immunity and infection [(21)]. And as seen in this paper, ECCA, VSS and inflammatory cell levels were lower in the OG than in the CG after treatment, indicating that the ultra-pulsed fractional CO_2 laser combined with topical EGF improved ECCA and VSS scores. The reason for this analysis is that EGF receptors activate the complexine kinase system and promote the process of skin wound tissue repair, thus accelerating epithelial cell proliferation and wound granulation tissue production, which in turn decreases wound healing time and contributes to skin barrier restoration, thereby reducing the level of inflammatory factors [(22)].

Moreover, the ultra-pulsed fractional CO_2 laser penetrates the damaged skin and is absorbed by the hemoglobin in the cells, causing the blood temperature to rise, prompting the damaged blood vessels to rupture and form thrombi, which are then absorbed and subside, inhibiting the inflammation, thus effectively improving the inflammatory cytokine levels and thus the scar state [(23)]. We believe that, while recombinant human EGF gel is basically similar to natural human EGF in structure and purity, it can promote the growth and development of fibroblasts, accelerate wound repair and maintain wound wetness, avoid uncontrolled collagen renewal and degradation, and significantly control the rate of scar generation [(24)].

The combination with the CO_2 laser has a synergistic effect, resulting in shorter and more definitive wound repair cycles. Meanwhile, recombinant human EGF gel can reduce the risk of adverse reactions because it can reduce trauma exudation, the trauma microenvironment is continuously protected, the inflammation is effectively inhibited, and granulation tissue and new capillaries are well generated [(25)]. This is also confirmed by the lower overall incidence of adverse reactions in the OG as seen in our comparison of the two groups of patients.

Nevertheless, due to the short study period, the limited number of cases we studied and the lack of evaluation of patient prognosis, we are currently unable to determine the long-term prognostic impact of EGF combined with CO_2 laser on facial acne scars. In the meantime, we can further evaluate the difference in patients' life treatment and psychology

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after treatment and provide a more definite reference for the overall value of EGF combined with CO_2 laser treatment. Later, we will also analyze the above limitations and the application of EGF combined with CO_2 laser in more depth.

CONCLUSION

EGF combined with CO_2 laser is effective in treating facial acne scars, which can effectively improve the scarring symptoms of patients and shorten the recovery period, as well as effectively inhibit the adverse effects of laser treatment, and has high clinical application. This may be related to the advantage that EGF has an excellent inhibitory effect on the inflammation and can promote granulation tissue and new capillary production.

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Author s' contributions: F.L., conceived and designed the project, wrote and revised the paper. L.L., generated and analyzed the data. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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

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