

Comparing the Healing Effects of *Arnebia euchroma* Ointment With Petrolatum on the Ulcers Caused by Fractional CO₂ Laser: A Single-Blinded Clinical Trial

Jale Aliasl¹; Fariba Khoshzaban^{1,*}; Behrooz Barikbin^{2,*}; Mohsen Naseri¹; Mohammad Kamalinejad³; Fatemeh Emadi¹; Zahra Razzaghi²; Daryush Talei⁴; Maryam Yousefi⁵; Fatemeh Aliasl⁶; Maryam Barati²; Parvaneh Mohseni-Moghaddam¹; Seyed Abbas Hasheminejad¹; Hossein Esmailzad Nami¹

¹Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, IR Iran

²Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

³Department of Pharmacognosy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

⁴Medicinal Plant Research Center, Shahed University, Tehran, IR Iran

⁵Skin Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran

⁶Department of Traditional Pharmacy, Faculty of Traditional Medicine, Tehran University of Medical Sciences, Tehran, IR Iran

*Corresponding Authors: Behrooz Barikbin, Laser Application in Medical Sciences Research Center, Shahid Beheshti University of Medical Sciences, Tehran, IR Iran. Tel: +98-2122741507, Fax: +98-2122744393, E-mail: bbarikbin@yahoo.com; Fariba Khoshzaban, Traditional Medicine Clinical Trial Research Center, Shahed University, Tehran, IR Iran. Tel: +98-2188964792, Fax: +98-2188966310, E-mail: fkshsh_99@yahoo.com

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Background: *Arnebia euchroma* ointment (AEO) has been used in Iranian traditional medicine for burn wound healing.

Objectives: The aim of this study is to evaluate wound healing efficacy of AEO in burn wounds after fractional CO₂ laser.

Patients and Methods: This split-face, single-blinded, single-center clinical study was performed in Shohada-e-Tajrish Hospital, Tehran, Iran. A total of 26 subjects with facial acne scar, who were to receive fractional CO₂ laser resurfacing were recruited. After laser procedure, AEO was applied to one side of the face and petrolatum on the other side for wound healing. Digital photographs were taken from acne scar area before resurfacing and on each of the assessment sessions. Three researchers, who were unaware of the applied medications, assessed these digital photographs for erythema, edema, epithelial confluence, crusting/scabbing, and general wound appearance. Subject's irritations such as dryness and itching were evaluated on the second, fifth, and seventh days.

Results: Our study indicated higher epithelial confluence and general wound appearance scores ($P = 0.045$ for both) and less erythema and edema on fifth day in petrolatum ($P = 0.009$ and $P = 0.034$, respectively). The results showed less crusting and erythema ($P = 0.016$ and $P = 0.035$, respectively) and higher general wound appearance scores in petrolatum on the second day ($P = 0.035$ and $P = 0.001$, respectively). Dryness was the most common subjective complaint in both groups; however, it was more severe in AEO, especially on the second day ($P = 0.023$).

Conclusions: Despite the healing effects of AEO in burn wounds, petrolatum was more effective than AEO in post-laser wound.

Keywords: Acne; *Arnebia*; Traditional Medicine; Laser; Wound Healing

1. Background

Acne is one of the most common diseases in adolescents that can lead to atrophic scars (1). There are many treatment modalities for acne scars (2). Ablative fractional carbon dioxide (CO₂) laser is the most frequently used (3) and the gold standard therapeutic method for acne scar (4). Ablative fractional resurfacing (AFR) is a combination of ablative technology and fractional photothermolysis (4). Fractional ablative laser creates microscopic columns injury, termed microscopic thermal zones (MTZs), on the dermis that are surrounded by columns of normal tissue. These microscopic lesions are healed very quickly with limited complications (5-7). AFR produces skin damage and removes the epidermis and variable portions of the

dermis (8). Topical ointments, cold compresses, and diluted solutions of acetic acid promote post-laser wound healing and reduce swelling (6, 9). Therapeutic effects of current treatments are not satisfactory and petrolatum is still the standard treatment for laser wound care (10). Treatment should speed up re-epithelialization and reduce rest time, with minimal irritation (11). Unfortunately, there is no standard care for post-laser resurfacing treatment of the face (6). Since ancient times, plants have been used as rich sources of effective and safe medicines. About 80% of world populations are still dependent on traditional medicines (12). *Arnebia euchroma* (Royle) Johnston from the Boraginaceae family grows in alpine

region, Asia (especially in Iran), Himalaya, and North Africa (13, 14). Its prominent components are shikonin and alkannin. They have widespread pharmacologic properties including anti-inflammatory and antimicrobial (15). *Arnebia euchroma* is known as Havachoobeh in Iranian traditional medicine (ITM) (16) and is named Abukhalsa in "Canon of Medicine" (written by Avicenna) (17). It is traditionally used to treat infective and burn wounds (17, 18). It has also pain relief properties (19). There are many topical compounds of *A. euchroma* for burn wounds healing in ITM, one of which is "Marhame Havachoobeh" (*A. euchroma* ointment [AEO]) (16).

2. Objectives

The purpose of this study was to determine the healing effects of AEO on post-laser wound healing in patients with acne scar in comparison with petrolatum. It was the first clinical trial that evaluated effects of *A. euchroma* compound on wound healing in patients with post-laser resurfacing acne scar.

3. Patients and Methods

3.1. Preparation of *Arnebia euchroma* Ointment

The dried roots of *A. euchroma* were purchased from local market in Tehran Bazaar, identified by Professor Gholamreza Amin, and were kept at the herbarium of faculty of pharmacy, Tehran University of Medicinal Sciences, under the voucher number PMP-216. AEO was made from *A. euchroma* roots (10 g), sesame (*Sesamum indicum*) oil (100 g), and Wax (10 g), with the weight ratio of 1:10:1 (16). The dried roots of *A. euchroma* were chopped and heated in sesame oil at 40°C to 60°C for 12 hours. Then samples were filtered and mixed with melted Wax and filled in tubes. Petrolatum was filled in similar tubes. Since the red color and smell of AEO was different from those of petrolatum, the blindness of patients was not possible.

3.2. Subjects and Intervention

This split-face, single-blind, single-center, clinical study was performed in Laser Research Center of Shahid Beheshti University of Medical Sciences, Shohada-e-Tajrish Hospital, Tehran, Iran. A total of 47 subjects with the Fitzpatrick skin phototype of II to IV, 20 to 65 years of age, and mild to severe bilateral facial atrophic acne scars, who referred for laser resurfacing, were evaluated to enroll in the study (The Fitzpatrick Scale [also Fitzpatrick skin typing test or Fitzpatrick photo typing scale] is a numerical classification schema for the color of skin. It remains a recognized tool for dermatologic research into the color of skin. It measures several components: Genetic Disposition, Reaction to Sun Exposure, and Tanning Habits. The Fitzpatrick Scale: Type I (scores 0-7) Light, pale white. (Always burns, never tans), Type II (scores 8-16) White; fair. (Usually burns, tans with difficulty), Type III (scores 17-24)

Medium, white to olive. (Sometimes mild burn, gradually tans to olive), Type IV (scores 25-30) Olive, moderate brown. (Rarely burns, tans with ease to a moderate brown), Type V (scores over 30) Brown, dark brown (Very rarely burns, tans very easily), Type VI Black, very dark brown to black. (Never burns, tans very easily, deeply pigmented). Subjects were excluded if they had any known allergy or sensitivity to lotions, moisturizers, creams, or healing ointments. In addition, pregnant women and subjects who received isotretinoin or topical drugs simultaneously or had active acne in faces were excluded. Written informed consent was obtained from each subject.

Before resurfacing, the patient's acne scar area was cleaned and a topical anesthetic mixture (lidocaine, prilocaine) was applied. Then, resurfacing was performed using a MIXEL-CO2 Fractional Laser system (Hironic Co, Ltd., Korea) with the following setting parameters: energy, 20 to 50 mJ; distance, 0.7 to 0.9 mm; and the number of passes, one to three depending on the severity of the acne scar. After fractional CO₂ laser resurfacing, cold compress was applied. AEO and petrolatum were used to opposite sides of the face four times a day (morning, midday, evening, and bedtime) for one week. The Ethics Committee of Shahed University approved the protocol (approval number: 148489). The study conformed to the Helsinki Declaration of 1975 and was registered in the Iranian Registry of Clinical Trials (No., IRCT201109067499N1).

3.3. Measurement of Wound Healing

Subjects visited on the second, fifth, and seventh days of procedure to take digital photographs and to be assessed for subjective irritation parameters (burning, itching, dryness, and pain) by using four-point grading scales (Table 1). Any adverse events including the presence of purulent discharge or infection were recorded. At the end of the study, three blinded expert researchers (dermatologist), who were unaware of assigned treatment to each side, observed digital photographs for assessment of wound-healing efficacy. Erythema, edema, crusting/scabbing, epithelial confluence, and general wound appearance were evaluated assessed using the five-point grading scales (Table 1) to determine the efficacy of wound healing.

3.4. Statistical Analysis

Sample size was determined according to the following formula:

$$N = (1/f) [2 (z_{1-\alpha} + z\beta)^2 (\sigma^2)/d^2]$$

With the power of 90%, the number of required patients to complete each treatment arm was calculated at 24. SPSS 16 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Results were reported as the mean \pm standard deviation. Chi square test was used for comparison of the frequency of variables between two groups. Student t test was used to compare quantitative variables. P value < 0.05 was considered as statistically significant.

4. Results

From February to June 2012, 47 subjects with mild to severe bilateral atrophic facial acne scars, who were referred for laser resurfacing, were enrolled. Three subjects who had active acne ($n = 2$) or received isotretinoin ($n = 1$) were excluded. Eighteen subjects discontinued their therapy. The main reasons of dropping out of the study were lack of effect, not attending for taking digital photographs, and personal reasons. Finally, 26 patients, 17 females (65.4%) and nine males (34.6%) completed the study. The mean age was 29 years (range, 20-50). In comparison to AEO, petrolatum showed significantly less erythema and crusting ($P = 0.035$, $P = 0.016$ respectively) and higher general wound appearance scores on the second day ($P = 0.001$) and less erythema and edema on the fifth day of therapy ($P = 0.009$ and $P = 0.034$, respectively) (Table 2). In addition, petrolatum had higher epithelial conflu-

ence and general wound appearance scores on the fifth day of therapy ($P = 0.045$ in both) (Table 2). Subjective assessments of irritation demonstrated no significant difference in erythema, edema, itching, burning, and pain between groups at any time point (Table 3). Both treatments showed good safety profile and there were no serious adverse reactions. The most common unpleasant complaints were dryness in both groups; however, it was more severe in AEO, especially at second day ($P = 0.023$) with no significant differences at the fifth and seventh days (Table 3). No incidence of purulent discharge or infection was seen with any of the study treatments. At the end of the study, 14 subjects (53.8%) judged the petrolatum treated side that looked better and only six (23%) preferred AEO ($P \leq 0.02$). Most patients did not like to use AEO on the other half of their faces because of its red color.

Table 1. Grading Score

Variable	Scale
Erythema	0 = None or Absent, 1 = Mild, 2 = Moderate, 3 = Marked, and 4 = Severe
Edema	0 = None or Absent, 1 = Mild, 2 = Moderate, 3 = Marked, and 4 = Severe
Epithelial Confluence	0 = None, 1 = Slight (Up to 30%), 2 = Moderate (31%-60%), 3 = Extensive (61%-90%), and 4 = Almost Complete (91%-100%)
Crusting/Scabbing	0 = None, 1 = Slight (Up to 29%), 2 = Moderate (30%-59%), 3 = Extensive (60%-90%), and 4 = Almost Complete (91%-100%)
General Wound Appearance	0 = Poor, 1 = Fair, 2 = Good, 3 = Very Good, and 4 = Excellent
Subjective Irritation	
Burning	0 = none or absent, 1 = mild, 2 = moderate, 3 = severe or extreme
Itching	0 = none or absent, 1 = mild, 2 = moderate, 3 = severe or extreme
Pain	0 = none or absent, 1 = mild, 2 = moderate, 3 = severe or extreme
Dryness	0 = none or absent, 1 = mild, 2 = moderate, 3 = severe or extreme

Table 2. Comparison of Treatments With *Arnebia euchroma* Ointment and Petrolatum in Clinical Grading Scores by Researchers^a

Day	Petrolatum	<i>Arnebia euchroma</i> Ointment	P Value
Erythema			
2	2.28 ± 0.61	2.62 ± 0.53	0.035 ^b
5	1.26 ± 0.40	1.63 ± 0.46	0.009 ^b
7	0.68 ± 0.58	0.70 ± 0.47	0.873
Edema			
2	1.13 ± 0.27	1.29 ± 0.34	0.071
5	0.58 ± 0.25	0.77 ± 0.27	0.034 ^b
7	0.09 ± 0.15	0.10 ± 0.21	0.789
Crusting/Scabbing			
2	1.21 ± 0.45	1.56 ± 0.54	0.016 ^b
5	0.79 ± 0.63	0.99 ± 0.64	0.362
7	0.25 ± 0.27	0.19 ± 0.28	0.473
Epithelial Confluence			
2	1.55 ± 0.32	1.39 ± 0.41	0.141
5	2.28 ± 0.41	1.98 ± 0.46	0.045 ^b
7	2.51 ± 0.30	2.54 ± 0.28	0.734
General Wound Appearance			
2	1.44 ± 0.26	0.88 ± 0.25	0.001 ^b
5	2.42 ± 0.42	2.14 ± 0.40	0.045 ^b
7	3.05 ± 0.42	2.99 ± 0.37	0.616

^aData are presented as mean ± SD.

^bSignificant at $P \leq 0.05$.

Table 3. Comparison of Treatments With *Arnebia euchroma* Ointment and Petrolatum by Subjects ^{a,b}

Day	Petrolatum	<i>Arnebia euchroma</i> Ointment	P Value
Dryness			
2	1.96 ± 0.95	2.65 ± 1.16	0.023 ^b
5	1.84 ± 1.15	2.42 ± 1.41	0.114
7	1.57 ± 1.06	2.03 ± 1.34	0.175
Itching			
2	1.88 ± 0.95	1.84 ± 0.88	0.876
5	1.53 ± 0.98	2.00 ± 1.13	0.124
7	1.15 ± 0.67	1.23 ± 0.65	0.678
Edema			
2	1.34 ± 0.79	1.46 ± 0.90	0.628
5	1.11 ± 0.65	1.26 ± 0.66	0.405
7	1.07 ± 0.62	1.11 ± 0.65	0.829
Erythema			
2	2.07 ± 1.12	2.57 ± 1.36	0.156
5	1.76 ± 1.21	2.19 ± 1.32	0.235
7	1.76 ± 1.06	2.07 ± 1.26	0.348
Pain			
2	1.38 ± 0.80	1.46 ± 0.81	0.733
5	0.92 ± 0.27	1.07 ± 0.27	0.742
7	1.03 ± 0.52	0.92 ± 0.27	1.000
Burning			
2	1.96 ± 1.03	2.19 ± 1.02	0.423
5	1.30 ± 0.61	1.42 ± 0.70	0.532
7	1.07 ± 0.27	1.03 ± 0.44	0.709
Discharge			
2	1.65 ± 0.97	1.50 ± 0.98	0.575
5	1.38 ± 0.85	1.42 ± 0.85	0.872
7	1.19 ± 0.49	1.15 ± 0.4	0.773

^a Data are presented as mean ± SD.^b Significant at P ≤ 0.05.

5. Discussion

The present study was the first clinical assessment of wound healing effect of AEO on post-laser resurfacing acne scar. AEO is traditionally used for wound healing (16, 17). *A. euchroma* has anti-inflammatory (14), antimicrobial (15), and burn wound healing effects (18). Despite the healing effects of *A. euchroma*, our study showed that it had no significant effect on post-laser wound in comparison with petrolatum. Some studies have evaluated the effect of *A. euchroma* on burn wound healing. In one experimental study, the healing effect of *A. euchroma* extract in second-degree burn wounds on rats was compared with and silver sulfadiazine. This study revealed that *A. euchroma* and silver sulfadiazine significantly improved re-epithelization, fibroblasts proliferation, and collagen bundle synthesis and had a remarkable anti-inflammatory effect. This study showed *A. euchroma* herbal extract was an effective treatment for second-degree burn wounds in comparison with silver sulfadiazine (18). In another experimental study, ef-

ficacy of *A. euchroma* on third-degree burn-wound was assessed in 48 female Sprague-Dawley rats and showed positive effects of *A. euchroma* (20). On the other hand, studies have shown that alkannin and shikonin, the main components of *A. euchroma*, were active against methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant enterococci (21). Shikonin is famous for its natural red-purple color and medicinal properties. It was used for curing burnt skin and ulcers in traditional medicine. Modern medicinal studies support its old-known uses and suggest additional applications in cancers and HIV (22). Another in vivo study on mouse skin tissues suggested that topical treatment with shikonin could exert a potent stimulatory effect on epithelial-mesenchymal transition and suppress the expression of the associated microRNAs in skin wound healing. Altogether, these cellular and molecular data provide further evidence in support of the specific pharmacologic effects of shikonin in wound healing and

immune modulation (23). There was no clinical study on the evaluation of wound healing effects of *A. euchroma* in post-laser resurfacing. However, there are some studies on post-laser wound healing assessment with another burn healing drugs. For example, a research compared Aquaphor healing ointment (AHO) (AHO is a formulation of 41% petrolatum, mineral oil, ceresin, lanolin alcohol, panthenol, glycerin, and bisabolol) with Biafine topical emulsion (BTE) (BTE ingredients include purified water, liquid paraffin, ethylene glycol monostearate, stearic acid, propylene glycol, paraffin wax, squalane oil, avocado oil, trolamine/sodium alginate, triethanolamine, cetyl palmitate, methylparaben [sodium salt], sorbic acid [potassium salt], propylparaben [sodium salt], and fragrance) on wound healing after fractional CO₂ laser resurfacing of the perioral area. Twenty patients applied AHO and BTE to opposite sides of their faces and results showed that AHO can be considered superior to BTE in accelerating healing in wound care after laser resurfacing in comparison with (11). Another clinical study was conducted to determine the effectiveness of Cicactive (CICA) gel in wound healing after resurfacing laser in comparison with 0.1% silver sulfadiazine cream (CICA gel is a hydrocolloid gel, which is composed of sodium alginate, hydroxypropylsilane, D-panthenol, comfrey great, zinc gluconate and Uriage 30% thermal water. This agent is fragrance-free, hypoallergic, and highly tolerable, which encourages wound healing and renewal of damaged epidermis. The gel suits for treatment of skin damage caused by mechanical reasons or after medical/dermatological treatment. Studies have shown that zinc gluconate accelerates keratinization and wound healing; however, its synergistic effect with D-panthenol enhances the latter function. D-panthenol is a variant of vitamin B₅, which significantly increases intracellular protein synthesis and cell renewal rate. Therefore, it decreases the duration of wound healing). CICA gel showed better results in improving wound healing than 0.1% silver sulfadiazine cream did (24). Silver sulfadiazine is applied as standard topical therapy for patients with partial-thickness burns (25) and BTE is used in the United States as a topical therapy for a variety of skin traumas including full-thickness wounds, pressure sores, first-degree and second-degree burns, and sunburns (11). Despite the effect of silver sulfadiazine and BTE on burn wound healing, these studies suggested that CICA gel and AHO could be considered as better topical agents for post-laser wounds.

We compared the effects of petrolatum with AEO in post-laser resurfacing wound and despite our anticipation, petrolatum was better than AEO was in this kind of wound. As a result, the standard and usual effective burn drugs had no good effect on post-laser resurfacing wound healing. We suggested some reasons for the unsatisfactory result of AEO. The first reason might be related to wound kind that was generated in AFR. This wound is different from flames and hot water wounds (26, 27). Another reason might be the combination of AEO and its components. Unfortunately, the compliance of AEO was

not good due to its color and the creation of dryness in patients' skin. Moreover, the sample size of our study was small. In ITM, imbalances in body temperament and humor lead to diseases and the drugs used for the treatment should possess the opposite temperament. For example a patient with hot mistemperament can be cured by a drug with cold temperament and vice versa (28). In Canon of Avicenna, effective drugs on burn wounds have a little dryness effects (17); therefore, they are not suitable for the treatment of post-laser wounds alone because laser-induced wound has a dry temperament. Since CO₂ laser vaporizes intracellular and extracellular water (29), the post-laser wound is drier than other burn wounds are. Based on the principles of ITM, drugs with moistening property must be used for laser wound treatment. Therefore, if burn drugs are combined with moistening materials, they can be ideally used for this type of wounds.

This study showed that AEO, an effective drug on burn wound healing that has been used by people for many years in many places (Iran and East of Asia), had no favorable healing effects on post-laser wounds in comparison with petrolatum. It seems that the usual burn drugs are not beneficial for the treatment of laser wounds alone, but if they are combined with moistening materials, eg, *Malva sylvestris*, they might have good healing effects on post-laser wound. More studies to evaluate the combination of *A. euchroma* with a moistening drug for post-AFR wound healing are suggested.

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Authors' Contributions

Study concept and design: Behrooz Barikbin, Mohsen Naseri, Fariba Khoshzaban, and Mohammad Kamalinejad; acquisition of data: Jale Aliasl, Fariba Khoshzaban, and Behrooz Barikbin; analysis and interpretation of data: Zahra Razzaghi and Daryush Talei; drafting the manuscript: Jale Aliasl; critical revision of the manuscript for important intellectual content: Behrooz Barikbin, Fariba Khoshzaban, Jale Aliasl, Fateme Emadi, Maryam Yousefi, Maryam Barati, Fateme Aliasl, and Parvaneh Mohseni Moghaddam; statistical analysis: Zahra Razzaghi and Daryush Talei; administrative, technical, and material support: Maryam Yousefi, Maryam Barati, Fateme Aliasl, Seyyed-Abbas Hasheminejad, Hossein and Esmailzad-Nami; study supervision: Fariba Khoshzaban and Behrooz Barikbin.

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