

The Efficacy of Topical Hyaluronic Acid Serum in Acne Scar Patients Treated with Fractional CO₂ Laser

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Abstract Acne is a common disorder experienced by up to 80% of people between 11 and 30 years of age and by up to 5% of older adults. It is caused by several factors including increased sebum production, follicular hypercornification, colonization with *Propionibacterium acnes*, and a lymphocytic and neutrophilic inflammatory response. Acne scarring can be divided into 2 main categories: Atrophic and Hypertrophic scars, the atrophic scars are subdivided into 3 basic types: icepick scars, rolling scars, and boxcar scars. Fractionated carbon dioxide (CO₂) laser resurfacing combines the concept of fractional photothermolysis with an ablative 10600-nm wavelength. This technology allows for the effective treatment of acne scars, reduced recovery periods and a significantly minimal side effect profile as compared to traditional CO₂ laser resurfacing. Hyaluronic acid is a carbohydrate occurring naturally in all living organisms. The biological functions include maintenance of the visco-elasticity of liquid connective tissues such as joint synovial and eye vitreous fluid, control of tissue hydration and water transport. This study is designed to evaluate the efficacy of using topical hyaluronic acid serum in patients with atrophic acne scars after treatment with fractional CO₂ laser. **Patients and Method:** Thirty six patients (26 females and 10 males) with moderate to severe atrophic acne scarring were included in this. The patients were divided randomly into two equal groups; one group was treated with CO₂ fractional ablative laser alone and the other group was treated with laser in addition to topical hyaluronic acid serum to compare the final results between the two groups and assess the effect of hyaluronic acid on wound healing and post-operative complications. Therapeutic outcomes were assessed by standardized digital photography. **Results:** The final results after 3 months according to dermatologists' assessment of level of improvement in response to treatment by CO₂ laser combined with topical hyaluronic acid were as follows: three patients (16.6%) reported excellent improvement, nine patients (50%) significant improvement, five patients (27.7%) moderate improvement and one patient (5.5%) showed mild improvement in the appearance of the acne scars. The results were significant as indicated by the *P* value which was 0.002. All participants reported mild side effects like pain, erythema and peeling and few patients suffered from edema and severe peeling but they were all tolerable and transient and last for approximately five days. **Conclusion:** The addition of hyaluronic acid to CO₂ laser resurfacing does not only enhance the effect of laser but also provides faster recovery time and fewer side effects when compared to the CO₂ laser resurfacing alone.

Keywords Hyaluronic acid, Acne scars, Fractional CO₂ laser

1. Introduction

Acne is a chronic inflammatory disease of pilosebaceous follicles, characterized by comedones, papules, pustules, nodules & often scars. It is caused by several factors including increased sebum production, follicular hypercornification, colonization with *Propionibacterium acnes*, and a lymphocytic and neutrophilic inflammatory response [1, 2]. Collagen and other tissue damage from the inflammation of acne leads to permanent skin texture changes and fibrosis. Dermal damage is more long lasting

and results in an increase or decrease of tissue and often worsens in appearance with age as a result of normal skin changes. The two main causes of acne scar formation can be broadly categorized as either a result of increased fibrous tissue formation or, the more common cause, loss or damage of tissue [3]. Treatment of the true scars resulting from acne must reflect several considerations by the physician. Cost of treatment, severity of lesions, physician goals, patient expectations, side-effect profiles, psychological or emotional effect to the patient, and prevention measures should all play a role [4]. There are numerous surgical options available for treatment of acne scars (Table 1).

Ablative lasers are technologies with high selectivity for water. Therefore, their action takes place mainly on the surface but the depth of action is certainly to be correlated

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to the intensity of the emitted energy and the diameter of the spot used [5]. CO₂ lasers, which present lower selectivity for water, besides causing ablation are also capable of determining a denaturation in the tissues surrounding the ablation and a thermal stimulus not coagulated for dermal protein. CO₂ lasers have a double effect: they promote the wound healing process and arouse an amplified production of myofibroblasts and matrix proteins such as hyaluronic acid [6]. Ablative lasers remain the gold standard in skin resurfacing and provide the greatest clinical improvements with the least number of treatments. However, because of the complete vaporization of the epidermis and variable coagulative damage to the dermis, healing time is prolonged and treatments carry significant associated risks [7, 8].

Table 1. Surgical Management of Acne Scars

Scar Type	Proposed Management
Icepick <3.5 mm	Punch excision
Icepick >3.5 mm	Elliptical excision
Boxcar	Punch elevation
Sinus tract or wide base	Skin graft
Rolling	“Subcision”
Hypertrophic or Keloid	Debulking

Hyaluronic acid (hyaluronan, HA) is a carbohydrate, more specifically a mucopolysaccharide, occurring naturally in all living organisms. The unique viscoelastic nature of HA along with its biocompatibility and non-immunogenicity has led to its use in a number of clinical applications [9]. HA’s viscoelastic matrix can act as a strong biocompatible support material and therefore is commonly used as growth scaffold in surgery, wound healing and embryology [10]. HA receptors are involved in cellular signal transduction; one receptor family includes the receptors CD44, and RHAMM [11, 12] (Receptor for HA-Mediated Mobility). These are considered to be the major HA receptor on most cell types [13] and they have been implicated in regulating cellular responses to growth factors and plays a role in cell migration, particularly for fibroblasts and smooth cells [14].

Topical application of HA may result in increased hydration of the stratum corneum and lead to the enhanced topical delivery of a concomitantly applied drug across this skin barrier [15]. Cosmetic uses of hyaluronic acid HA has been extensively utilized in cosmetic products because of its viscoelastic properties and excellent biocompatibility [16]. Application of HA containing cosmetic products to the skin is reported to moisturize and restore elasticity thereby achieving an anti-wrinkle effect, albeit no rigorous scientific proof exists to substantiate this claim [17]. HA-based cosmetic formulations or sunscreens may also be capable of protecting the skin against ultraviolet irradiation due to the free radical scavenging properties of HA [18]. HA, either in a stabilized form or in combination with other polymers, is used as a component of commercial dermal

fillers in cosmetic surgery. HA degradation products are purported to contribute to scar formation. When hyaluronidase is added to generate HA fragments, there is increased scar formation [19]. These data support the theory that high molecular weight HA promotes cell quiescence and supports tissue integrity, whereas generation of HA breakdown products is a signal that injury has occurred and initiates an inflammatory response [20].

This study is designed to evaluate the efficacy of using topical hyaluronic acid serum in patients with atrophic acne scars after treatment with fractional CO₂ laser.

2. Patients and Methods

This is an open therapeutic trial study performed at Beirut Private Center for Laser Treatments in Baghdad, Iraq during the period from April, 1st 2015 to April, 1st 2016. Thirty six patients (26 females and 10 males) with moderate to severe atrophic acne scarring according to Goodman's qualitative global acne scarring grading system (table 8) were included in this study. Their ages ranged from 20 to 43 years (mean age: 29.69 years old SD±7.21) and their Fitzpatrick skin types were III-IV. This study approved by the ethical committee in Al-Kindy teaching hospital. Written informed consent was obtained from each patient.

Exclusion criteria include known photosensitivity, pregnancy or lactation, inflammatory skin disorders or active herpes infection, history of hypertrophic or keloidal scarring, and the use of isotretinoin or other physical acne treatments over the past 6 months. The use of anti-coagulants, isotretinoin, patients who had any medical illness (e.g. diabetes, chronic infections, blood dyscrasias) that could influence the wound healing process were also excluded. Patients were allowed to continue previous acne medications during the study except isotretinoin.

All patients had mixed types of atrophic acne scars, including ice pick, boxcar, and rolling scars, although, some particular type predominates and therefore is used to classify the patients accordingly (Table 2).

Table 2. Patients Predominant Scars Types

Patients Number	Type of scar
7 (19%)	significant rolling
14 (40%)	shallow boxcar
6 (16%)	Deep boxcar
9 (25%)	icepick scars

The whole procedure was fully explained and thoroughly discussed with the patients about the mechanism of laser treatment, the time required for the treatment, the behavior after the laser treatment, and the prospects of successful treatment and any unrealistic expectations of the end results were strongly discouraged. The patients were informed about all risks that may be caused by the laser treatment and the pre- and post-operative care.

The patients were divided randomly into two equal groups;

one group was treated with CO₂ fractional ablative laser and the other group was treated with laser in addition to topical hyaluronic acid serum to compare the final results between the two groups and assess the effect of hyaluronic acid on wound healing and post-operative complications.

The patients in the second group were asked to apply hyaluronic acid serum (1% sodium hyaluronate serum) to the face twice daily for a month prior to the laser peel in order to condition the skin before the procedure and for three months after the laser peel. The serum was formulated with 1% high molecular weight (about 1000 kDa), pharmaceutical grade and bioengineered hyaluronic acid. Before the application of the product, the patients were asked to cleanse the skin using a gentle cleanser and a good sun protection was highly encouraged.

Prior to each treatment, the face was cleansed with a mild non-abrasive detergent and gauzes soaked in 70% isopropyl alcohol. A topical anesthetic cream (EMLA, a eutectic mixture of local anesthesia of 2.5% lidocaine and 2.5% prilocaine, AstraZenica LP, Wilmington DE) was applied under an occlusive dressing for 1 hour and subsequently washed off to obtain completely dry skin surface. Eyes were protected with opaque goggles. Systemic antiviral therapy (acyclovir 400 mg twice daily) prescribed for each patient the night before operation as prophylaxis and for five days post operatively as well as topical antibiotics and a moisturizing cream, the patients were informed to apply a sunscreen for six weeks.

Three photos were taken before treatment for each patient for both sides and the front of the face with a digital camera (Sony DSC-T99 Cyber-shot® Digital Camera, 14.1 megapixel HD) and another set of photos was taken in each visit post-treatment using identical camera settings, lighting, and patient positioning. Systemic Antibiotics and Antiviral prescribed for each patients.

Fractional CO₂ laser was delivered to the areas with treatment parameters that has been adjusted based on the scar severity and each patient's tolerability. These parameters are:

1. The depth to which the laser will reach. We used 1 mm to 7 mm according to scar depth;
2. The distance between each spots of laser beams. We used 1 to 4 mm according to scar size;
3. The power which is the laser energy in mJ we used 30 to 70mJ according to scar severity.

The number of each passes (laser application) depends on depth of the scar (more depth need more passes). Smoke evacuator and a forced air cooling system (Zimmer Medizin Systemme, Cryo version 6) accompanied the procedure to improve patients comfort and compliance.

Patients were asked to return for medical assessment two weeks after operation then followed up monthly for 3 months.

Therapeutic outcomes were assessed by standardized

digital photography by the patient himself and by two blinded dermatologists. The dermatologists' evaluation and self-assessment level of improvement of the patients were evaluated using the following five-point scale:

- 0=no change;
- 1=slight improvement (0–25%);
- 2=moderate improvement (26–50%);
- 3=significant improvement (51–75%);
- 4=excellent improvement (>75%).

The two assessors were blinded to the order of the photographs. The evaluators were asked to perform two actions. First, to identify the photograph that showed better scar appearance. Second, to rate the difference in the severity of the acne scars using the above mentioned scale.

In addition, the participants were asked to report any cutaneous or systemic side effects associated with laser treatment particularly erythema, edema, crusts and erosions and pain. A scale of 0–3 was used to determine the level of discomfort from side effects during and after the procedure as following:

- 1=mild
- 2=moderate
- 3=severe

Analgesics and Sunscreens prescribed to the patients post-treatment and the patients advised for strict sun protection particularly during the first ten post-treatment days.

Statistical data were analyzed by *Chi test* and *P* value < 0.05 is considered statistically significant descriptive data by frequency, percent, figure and table.

3. Results

Thirty six patients (26 females and 10 males) were included in the study. All patients completed the study, including the 3- month follow-up period. Most patients had mixed types of atrophic acne scars, including ice pick, boxcar, and rolling scars.

The patients were divided equally into two groups (18 patients in each group). First group was treated with CO₂ fractional ablative laser alone and the second group was treated with laser in addition to topical hyaluronic acid serum.

In the second group, according to the patients' self-assessment of improvement, the results were remarkable and showed a great amount of satisfaction (Table 3). The results after 3 months follow-up were as the following: three patients (16.6%) reported excellent improvement, eight patients (44.4%) significant improvement, four patients (22.2%) moderate improvement and three patients (16.6%) mild improvement in the appearance of the acne scars. The results considered significant as indicated by the *P* value which was 0.001.

Table 3. Patients' Self-Assessment of Level of Improvement in Response to Treatment by CO₂ Laser Combined with Topical Hyaluronic Acid

	Score	1	2	3	4	<i>P</i> value
wk	1 wk	7 (38.8%)	9 (50%)	2 (11.1%)	-	0.001
	4 wk	6 (33.3%)	8 (44.4%)	3 (16.6%)	1 (5.5%)	
	8 wk	4 (22.2%)	5 (27.7%)	6 (33.3%)	3 (16.6%)	
	12 wk	3 (16.6%)	4 (22.2%)	8 (44.4%)	3 (16.6%)	

Table 4. Dermatologists' Assessment of Level of Improvement in Response to Treatment by CO₂ Laser Combined with Topical Hyaluronic Acid

	Score	1	2	3	4	<i>P</i> value
wk	1 wk	6 (33.3%)	8 (44.4%)	3 (16.6%)	1 (5.5%)	0.002
	4 wk	5 (27.7%)	7 (38.8%)	4 (22.2%)	2 (11.1%)	
	8 wk	2 (11.1%)	3 (16.6%)	8 (44.4%)	4 (22.2%)	
	12 wk	1 (5.5%)	5 (27.7%)	9 (50%)	3 (16.6%)	

Table 5. Dermatologists' Assessment of Level of Improvement in Response to Treatment by CO₂ Laser Alone

	Score	1	2	3	4	<i>P</i> value
wk	1 wk	6 (33.3%)	7 (38.8%)	4 (22.2%)	1 (5.5%)	0.002
	4 wk	5 (27.7%)	8 (44.4%)	4 (22.2%)	1 (5.5%)	
	8 wk	3 (16.6%)	6 (33.3%)	6 (33.3%)	3 (16.6%)	
	12 wk	2 (11.1%)	5 (27.7%)	8 (44.4%)	3 (16.6%)	

Table 6. Patients' Self-Assessment of Level of Improvement in Response to Treatment by CO₂ Laser Alone

	Score	1	2	3	4	<i>P</i> value
wk	1 wk	11 (61.1%)	7 (38.8%)	-	-	0.001
	4 wk	9 (50%)	8 (44.4%)	1 (5.5%)	-	
	8 wk	8 (44.4%)	6 (33.3%)	3 (16.6%)	1 (5.5%)	
	12 wk	5 (27.7%)	6 (33.3%)	4 (22.2%)	3 (16.6%)	

According to dermatologists' assessment of the results of patients in the second group (Table 4), the results improved dramatically from 5.5% in 1st week to 16.6% for excellent improvement after 3 months. Significant improvement group shows the major response and increase from 16.6% after 1 week to 50% after 3 months, it gives us a strong indicator of the overall results.

The final results after 3 months were as follows: three patients (16.6%) reported excellent improvement, nine patients (50%) significant improvement, five patients (27.7%) moderate improvement and one patient (5.5%) showed mild improvement in the appearance of the acne scars. The results were significant as indicated by the *P* value which was 0.002.

The first group of patients (those were treated with laser alone) shows a different level of improvement according to dermatologists' assessment (Table 5) and patients' self-assessment (table 6). After three months the results (according to dermatologists' assessment) were as following: three patients (16.6%) reported excellent improvement, eight patients (44.4%) significant improvement, five patients (27.7%) moderate improvement and two patients (11.1%) mild improvement in the appearance of the acne scars. The results were significant as indicated by the *P* value which was 0.002.

The results after three months according to patients' self-assessment were as following: three patients (16.6%) reported excellent improvement, four patients (22.2%) significant improvement, six patients (33.3%) moderate improvement and five patients (27.7%) mild improvement in the appearance of the acne scars. The results were significant as indicated by the *P* value which was 0.001.

The laser treatment was generally well tolerated. All participants underwent treatment-related pain, but there was no need for extra anesthesia. All participants reported mild erythema for approximately 2-3 days but some of them experienced severe erythema especially in patients who have been treated with laser alone. Eight patients (44.4%) reported edema after 24 hours following laser treatment with hyaluronic acid that lasted for five days compared to laser treatment alone (83.3%) and lasted for ten days. Peeling occurs from the third day and completed in the fifth day in the majority of patients subjected to combination treatment and in 16.6% last for 7 days, while it lasts for 10 days in patients treated with laser alone. Social activity could commence as early as 7 days after the laser treatment combined with hyaluronic acid while it takes 14 days to return to normal social life in patients treated with laser alone. Other possible adverse events related to laser treatment in general, such as pigmentary alterations (hyperpigmentation),

bleeding, vesiculation, crust, scarring, and infection were not observed. (Tables 7-8).

Figures 1-4 showed sample results of second group after adding hyaluronic acid to laser treated patients after three months as compared to pre-operative states.

Table 7. Adverse Effects Related to Treatment by Fractional CO2 Laser With and Without Topical Hyaluronic Acid

Adverse effects	No. & percent of patients without HA	No. & percent of patients with HA
treatment-related pain	(18) 100%	(18) 100%
mild erythema	(18) 100%	(18) 100%
Severe erythema	(6) 33.3%	(2) 11.1%
Edema	(15) 83.3%	(8) 44.4%
Severe peeling	(6) 33.3%	(3) 16.6%
Bleeding	-	-
Hyperpigmentation	-	-
Vesiculation	-	-
Crust	-	-
Scarring	-	-
Infection	-	-

Table 8. Recovery Time Related to Treatment by Fractional CO2 Laser With and Without Topical Hyaluronic Acid

Parameters	Recovery time in patients without HA	Recovery time in patients with HA
Erythema	5 days	3 days
Edema	10 days	5 days
Peeling	12 days	6 days
Social activity	14 days	7 days



Figure 1. Patient 1: Pre- and 3 months post operatively

within the body [22]; however, the levels of free hyaluronan within the blood are low due to its rapid clearance by the liver [23].



Figure 2. Patient 2: Pre- and 3 months post operatively

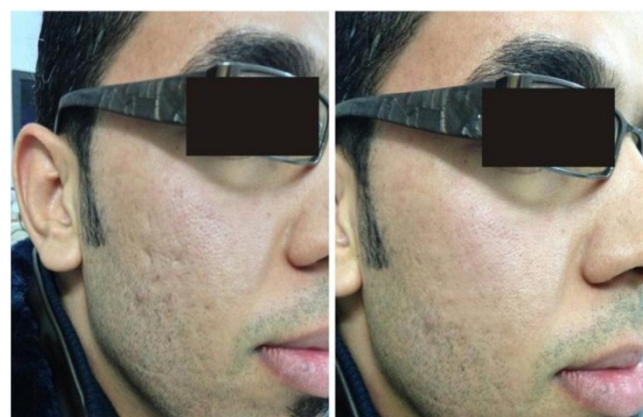


Figure 3. Patient 3: Pre- and 3 months post operatively



Figure 4. Patient 4: Pre- and 3 months post operatively

4. Discussion

Hyaluronan is a synthesized polysaccharide polymer composed of chains of the monosaccharide glucuronic acid and N-acetylglucosamine-1. A large variety of cells are able to produce hyaluronan; however, the most important, in terms of the wound healing response, appears to be keratinocytes, fibroblasts and platelets [21]. The skin normally contains the highest concentration of hyaluronan

During tissue trauma or following infection, hyaluronan accumulates and stimulates immune cells at the injury site to express inflammatory mediators [24-26]; higher levels were also found in newly formed granulation tissue [27]. Hyaluronan is a highly hygroscopic (moisture retaining) compound [28]; By maintaining a moist wound environment, hyaluronan protects cells from the effects of desiccation, also assisting in cell movement by helping the dividing cell to

disassociate itself from its substratum and providing a hydrated matrix, which facilitates easier cell movement [29]. In addition, it also affects the migration of fibroblasts to the wound site [30] by interaction with hyaluronan receptors (CD44 and RHAMM) through which it activates intracellular signaling pathways [31].

Atrophic acne scars occur as a consequence of impaired resolution or wound healing after the damage of sebaceous follicles during active inflammation [32], and are usually classified into ice pick, rolling, and boxcar scars according to shape and depth [33]. Their treatment options include laser skin resurfacing, chemical peeling, dermabrasion/microdermabrasion, tissue augmentation, and various other modalities.

Fractional photothermolysis (FP) is a relatively new technology for skin resurfacing introduced and discussed in 2004 [34]. It depends on generating multiple non-contiguous zones of thermal damage (MTZ) in the epidermis and dermis, sparing the viable tissue surrounding each MTZ. The untreated healthy skin remains intact and actually aids the repair process, promoting rapid healing with only a day or two of downtime [35]. FP stimulates epidermal turnover and dermal collagen remodelling, which leads to significant improvements in a variety of scars [36, 37]. This technology has been used in a wide variety of skin conditions including (but not limited to) photo-aging, periorbital wrinkling, acne scarring, melasma and other pigmented lesions [38].

The results of first group was very satisfactory as nearly as 72% of patients showed moderate to significant response according to dermatologists' assessment. These results were comparable to the results of another study investigating the effect of CO₂ laser in treating acne scars conducted in Iraq few years earlier [39]. The results are significant as indicated by the *P* values which was 0.002.

The results of the second group were very good as more than 77% of patients showed moderate to significant improvement. However, the patients' self-assessment is lower than that of the dermatologists (66%); this might be attributed to the fact that the patients usually use more subjective than objective scales, and they show a higher level of expectations of end results than the actual outcome. The results of both assessment groups (the patients and the dermatologists) are significant as indicated by the *P* values which were 0.001 and 0.002 respectively.

All patients show different level of improvement ranging from mild to excellent results after only one session of laser treatment. In fact, surprisingly, mild improvement was observed in only one patient according to the dermatologists' assessment, although; according to patients' self-assessment the results were less remarkable (as mentioned above). This gives us a strong indicator of the overall results and the level of improvement noticed by the patients in general.

The final outcome of laser treatment is best read after 3-6 months post-operatively. This time is usually needed for new collagen remodelling [40] and it was the same time interval we use to follow up our patients and read their end-results which were significantly different from the results after one

week post-operatively.

The effect of the addition of topical hyaluronic acid to the patients in combination with laser treatment is very obvious. According to previous studies investigating the effect of fractional ablative CO₂ laser on acne scars, 70% of the CO₂ laser sites were graded as having moderate to significant improvement of scars [39, 41]. Their end-results, although; were not significantly different from our results after 3 months follow-up (77% showed moderate to significant improvement) but taking in consideration the post-operative pain, edema, erythema and duration of peeling which were less and more tolerable and acceptable than that were associated with CO₂ laser treatment alone.

In contrast to CO₂ laser resurfacing alone, the physiologic changes in wound healing treated with hyaluronan serum will allow the skin to recover faster [42]. Pigment alteration, which is a common side effect of CO₂ laser, was not reported with hyaluronan addition in any of our patients even with those who don't commit to strict sunscreen.

It was clearly demonstrate that hyaluronic acid offers not only beneficial effects to the skin but also influence the expression of many genes including those contributing to keratinocyte differentiation and formation of intercellular tight junction complexes which are reported to be reduced in aged and photodamaged skin [43]. HA has been shown to promote the migration and maturation of keratinocytes in process of re-epithelialization and it has even been proposed as a possible marker for effective healing in soft tissues [44]. Its activity is manifested in granulation tissue where it is abundantly produced and counters the damage induced by reactive oxygen intermediates [45]. Hyaluronan has an active role in the modification of the inflammatory response. It is thought to moderate the inflammatory response through its specific interactions with constituents of the inflammatory response, stabilizing cytokine activity and reducing protease-induced damage [46].

In procedures aiming at aesthetic improvement, patient perception of the treatment outcome appears to be most important because it has a direct impact on patients' body image and self-esteem [47], which can be obtained superbly by the CO₂ laser but when hyaluronic acid topical serum is added, the results are noteworthy, recovery time is considerably shortened and traditional post-resurfacing sequelae are absent. Consequently this allows the patients a rapid return to their social or work environment.

In general, the addition of hyaluronic acid to CO₂ laser resurfacing does not only enhance the effect of laser but also provides faster recovery time and fewer side effects when compared to the CO₂ laser resurfacing alone.

5. Conclusions

1. Fractional CO₂ photothermolysis can be a safe and effective option for the treatment of acne scars in Iraqi skin.
2. Combination treatment with topical hyaluronic acid serum can constitute a synergistic approach for

optimal outcomes.

3. Fractional CO₂ photothermolysis plus topical hyaluronic acid serum were associated with substantial improvement in the appearance of all types of acne scars with lesser side effects.
4. Most patients began to show a visible improvement following only one session and according to visual assessments of patients and dermatologists, patients improvement continue to occur even after 3 months of operation.

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