Efficacy and safety of microneedling with and without platelet-rich plasma versus fractional CO_2 laser for treatment of acne scars: a randomized clinical trial

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Received: 11 June 2020
Accepted: 22 April 2021

Background: Acne scarring can significantly affect patients' quality of life, particularly when it involves the face. This study aimed to compare the efficacy of microneedling with and without platelet-rich plasma (PRP) versus fractional CO_2 laser therapy in treating acne scarring.

Methods: This randomized clinical study was performed on 90 patients with acne scarring. All the patients were divided into three groups (n = 30 per each): group A received microneedling, group B received microneedling plus PRP, and group C was treated by fractional CO_2 laser. Each patient underwent three treatment sessions across three-week intervals. The severity and depth of acne scars were graded using Goodman and Baron's scale and Visio Face systems, respectively.

Results: Out of 90 patients, 30 in group A, 22 in group B, and 26 in group C completed the trial. Analysis was done based on the per-protocol method on a total of 78 patients. Regarding the severity of acne scarring, significantly better results were obtained for groups A and B than for group C ($P \leq 0.001$), while no meaningful difference was seen between groups A and B. Also, there was a significant difference between group B and other groups in terms of patients' satisfaction ($P = 0.04$). The Visio Face systems showed that the depth of acne scars in group B had better improvement than in other groups ($P = 0.02$).

Conclusion: Microneedling plus PRP led to the most patient satisfaction and highest improvement in acne scar depth. However, considering the fewer side effects and acceptable cost-benefit profile of microneedling alone compared with fractional CO_2 laser or microneedling plus PRP, isolated microneedling could be considered the first choice for treating acne scars.

Keywords: acne scar, microneedling, platelet-rich plasma, fractional CO_2 laser

Iran J Dermatol 2022; 25: 91-98

DOI: 10.22034/IJD.2021.234797.1123

INTRODUCTION

Acne is one of the most common complaints among those referring to dermatologists. The main sequel of acne is scarring, related to the severity and natural course of the disease as well as individual predisposition [1,2]. Since the face is where acne scars manifest most, it could threaten patients' quality of life. Hence, scarring is one of the most important treatment challenges [3,4]. To

resolve this issue, there are various treatment options such as dermabrasion, microdermabrasion, chemical peeling, and laser therapy [2,5-7].

Platelet-rich plasma (PRP) refers to a small volume of autologous plasma platelet concentration products that have been used and studied since the 1970s [8]. PRP provokes collagen production in the skin [9]. Indeed, regeneration occurs with PRP injection, resulting in healthier skin; this may be an ideal treatment for cutaneous injuries, especially acne scars [10].

Fractional carbon dioxide (CO_2) laser induces thermal damage in the skin by creating microscopic thermal channels, which smoothen the skin through ablation and re-epithelialization, decreasing the severity of scars via collagen regeneration [11]. Despite the beneficial effect of fractional CO_2 laser in treating acne scars, its disadvantages (e.g., prolonged periods of inflammation of the skin and swelling) might cause dissatisfaction and disruption in the everyday life of patients, leading to the limited application of this technique [12,13]. Moreover, a recent study [14] has reported some risks associated with the use of fractional CO_2 lasers. These risks differ in severity and can be prolonged, especially in skin types IV and VI.

Recently, novel techniques have emerged, paving the way for successful results and a high level of patient satisfaction. One of the new therapies is microneedling or collagen induction therapy [2]. In this minimally invasive method, controlled skin puncturing by rolling with fine needles releases several growth factors that promote the normal wound healing process [15-17]. Treatment with microneedling, along with PRP and/or topical antioxidants, has emerged as a suitable choice for dermatological applications [18]. Accordingly, it could be used as an effective treatment of facial scars.

The main purpose of the present study was to investigate and compare the efficiency of three methods, namely microneedling, microneedling plus PRP, and fractional CO_2 laser, in treating acne scars, thereby arriving at the most effective and beneficial treatment for patients.

PARTICIPANTS AND METHODS

Sample size calculation

According to previous studies, the mean improvement in acne scar was 73.11 ± 9.5 and 5.6 ± 2.6, respectively, in two groups undergoing the needling and a combination of needling and laser. The required sample size was 28 in each group according to a confidence coefficient of 0.05 and a study power of 90%. Considering the probability of at least 10% drop out, 30 subjects were finally included in each group of the study. Z2 = 1.29, Z1 = 1.96, S2 = 6.2, S1 = 5.9, μ1 = 11.73, μ2 = 6.5.

Patients

This study was a randomized clinical trial (IRCT2015110318210n6) conducted on 90 patients with acne scars with similar age and gender distribution who attended the Skin Clinic of Rasool Akram Medical Complex. The inclusion criteria were the desire of patients to participate in the study and also their intention to adhere to the therapy.

Patients filled out the consent forms before inclusion in the study. The exclusion criteria included smoking, diabetes, platelet dysfunction, thrombocytopenia (platelet count below 50,000), chronic infections, hemodynamic instability, local inflammatory skin dysfunction or active herpes infection at the site of the procedure, consumption of anticoagulation or nonsteroidal anti-inflammatory drugs (NSAIDs) within 48 hours before the treatment, systemic corticosteroid use within 10 weeks before the treatment, hemoglobin of less than 10, fever, and a history of cancer (especially leukemia).

Study design

Patients were randomly divided into three groups of 30 patients as follows:

Group A was treated with three sessions of microneedling across three-week intervals. The microneedling was performed by Dermapen apparatus with special needles with a speed level of 45-50 and a needle penetration depth of 1-1.25 mm based on the location of thick or thin scars in the target site.

Group B was treated with three sessions of microneedling plus PRP. The PRP was prepared according to the following standard procedure: A 20 ml blood sample was taken from the patient. Blood samples were centrifuged at a revolution of 3400, and about 3-5 ml of plasma/platelet extract was taken and was topically poured on the patient face.

Then, the rotational movements were performed on the face using the microneedling apparatus.

Group C received fractional CO_2 laser using the Deka CO_2 apparatus with a power of 18-20, STACK2 density of 0.8, and pulse width of 1000-1200 microseconds. The apparatus's energy spectrum was from 18 to 20 based on the scar depth.

All three groups of patients were recommended to use sunscreen and avoid sunlight exposure as much as possible during the week after each session. We prescribed zinc oxide ointment as a healer and sunscreen for the first 48 hours for those who received microneedling and for the first week in group C.

Data collection

Data collection was based on a checklist including a part of patient information about patient characteristics, age, other diseases, and patient satisfaction after the treatment in percentages.

Also, all patients underwent photographic at each first visit, during each scheduled time, and three months after the last visit. The degrees of change and severity of acne scars were examined based on Goodman and Baron's system by a specialist blinded to the study groups. Also, complications and satisfaction rates were reported in each session. Goodman and Baron grading is simple and universally accepted. According to this classification, four different grades can be used to identify an acne scar, as shown in Table 1.

Grading the healing of acne scars was subjected to the Visio Face system regarding both qualitative and quantitative assessments. This system allows for a qualitative assessment by performing high-quality photography, ultimately examined through the blind method by another physician. The quantitative evaluation of scars was done by the Visio Face apparatus. Also, possible side effects were recorded in all groups.

Statistical analysis

Data analysis was performed using the statistical software SPSS 16.0.0 (SPSS Inc. Chicago, IL, USA). P-values less than 0.05 were considered significant. Shapiro-Wilk test was applied to test the normality assumption. Results were presented as median with total and interquartile ranges (IQR) or mean ± standard deviation (SD) for quantitative variables and were summarized by absolute frequencies and percentages for qualitative variables. The Kruskal-Wallis test was applied to examine the difference in patient satisfaction scores among the three groups. The pairwise comparison was applied using the Mann-Whitney U-test. Generalized Estimating Equation (GEE) models were fitted to examine the associations between type of therapy and change in acne scarring severity scores and depth of the acne scars over time. GEE models included two main effects (type of treatment and time) and the interaction of these effects. Time points in the analyses included baseline and three months after the last session. Using GEE, the correlation of multiple measurements within one patient was taken into account. A *P*-value less than 0.05 was considered significant.

RESULTS

Seventy-eight patients with acne scars completed

Table 1. Grades of acne scars

Grades of post-acne scarring	Level of disease	Clinical features
1	Macular	These scars can be erythematous, hyper- or hypopigmented flat marks. They do not represent a problem of contour like other scar grades but of color.
2	Mild	Mild atrophy or hypertrophic scars that may not be obvious at social distances of 50 cm or greater and may be covered adequately by makeup or the normal shadow of shaved beard hair in men or normal body hair if extra facial.
3	Moderate	Moderate atrophic or hypertrophic scarring that is obvious at social distances of 50 cm or greater and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extra-facial, but is still able to be flattened by manual stretching of the skin (if atrophic).
4	Severe	Severe atrophic or hypertrophic scarring that is evident at social distances greater than 50 cm and is not covered easily by makeup or the normal shadow of shaved beard hair in men or body hair if extra-facial and is not able to be flattened by manual stretching of the skin.

the study: 22 in the microneedling plus PRP group, 30 patients in the microneedling group, and 26 in the ablative fractional CO_2 laser group. The study process is illustrated in Figure 1. The study participants' baseline demographics and clinical characteristics are summarized in Table 2. The mean acne scarring severity score for the three study groups is presented in Table 3. In all

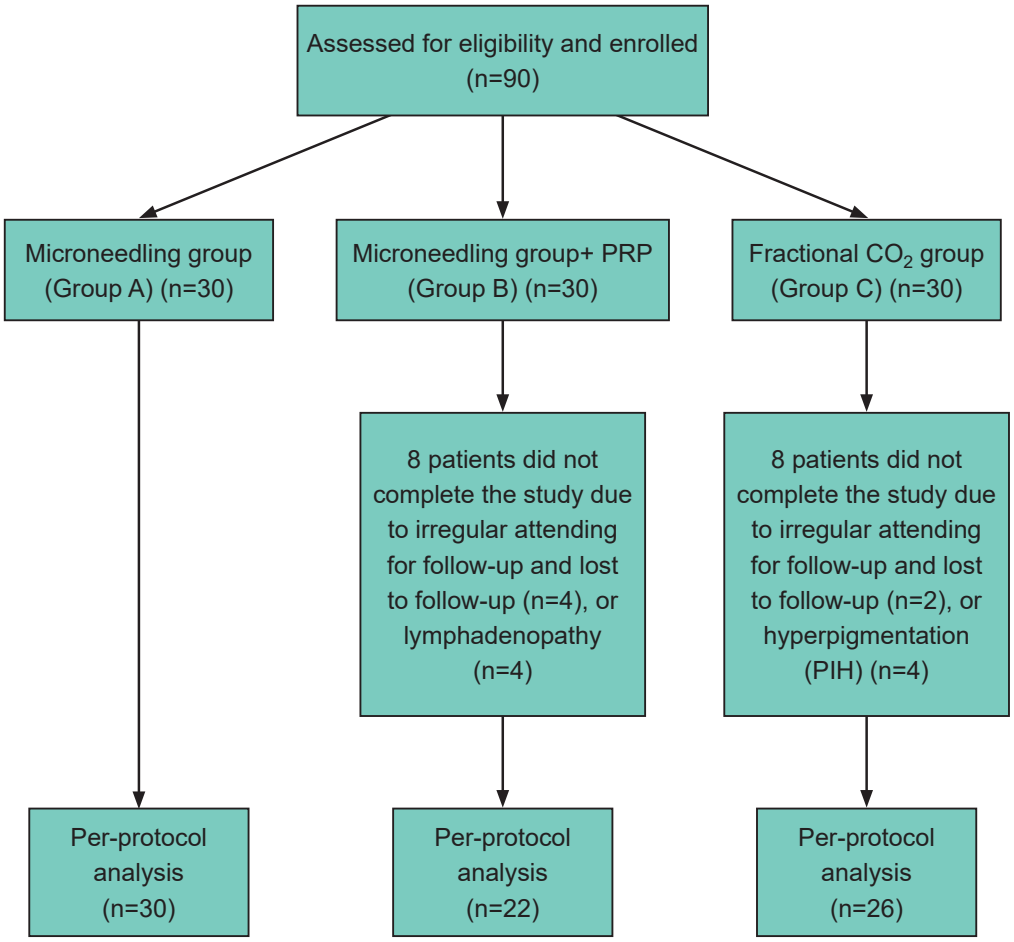

Figure 1. The flow diagram of the clinical trial

Table 2. Baseline demographics and clinical characteristics of the study participants

Characteristic	Microneedling+PRP group (n=22)	Microneedling group (n=30)	Fractional CO_2 laser group (n=26)
Gender, no. (%)			
Female	21 (95.45%)	23 (76.67%)	19 (73.08%)
Male	1 (4.55%)	7 (23.33%)	7 (26.92%)
Age, years	32.95 ± 8.20	32.73 ± 7.88	29.64 ± 6.27
Duration of acne, years	10 (5.8 to 15); (1.2 to 25)	10 (3 to 13.5); (2 to 23)	5.5 (3 to 10.5); (2 to 15)
Acne treatment, no. (%)			
Hormonal therapy	6 (27.27%)	5 (16.67%)	4 (15.38%)
Topical therapy	2 (9.09%)	0 (0.00%)	0 (0.00%)
Systemic antibiotics	12 (54.54%)	15 (50.00%)	12 (46.15%)
Systemic retinoids	5 (22.73%)	10 (33.33%)	2 (7.69%)
Without treatment	2 (9.09%)	6 (20.00%)	10 (38.46%)

Data are expressed as mean ± SD or median (IQR);(range) unless otherwise stated.
Abbreviations: IQR, Interquartile range (25^{th}-75^{th} percentiles)

Table 3. Acne scarring severity scores and depth of the scars over time among the three study groups

	Baseline	Three months after the last session	*P*-value*
Acne scarring severity scores			
Microneedling plus PRP group	10.09 (0.54)	4.64 (0.42) £	
Microneedling group	9.90 (0.60)	4.60 (0.42) £	< .0001
Ablative fractional CO_2 laser	6.23 (0.56)	3.00 (0.38) £	
Depth, mm			
Microneedling plus PRP group	16.68 (1.14)	8.64 (0.66) £	
Microneedling group	13.53 (0.65)	8.07 (0.47) £	< .0001
Ablative fractional CO_2 laser	13.50 (0.57)	10.04 (0.68) £	

* The P-value for Group×Time interaction (Based on the results of GEE analysis)
The values are expressed as mean (SE).
Note. Acne scarring severity scores are according to Goodman and Baron's quantitative acne scar grading system
Abbreviations: PRP, Platelet Rich-Plasma; mm, millimeter
£ $P < 0.05$ for a statistical difference from baseline to three months after the last session within the group.

groups, the mean acne scarring severity score fell significantly from baseline to three months after the last session (Table 3).

Compared to the fractional CO_2 laser group, the microneedling plus PRP group had a greater reduction in the acne scarring severity score from baseline to three months after the last session (mean difference 2.22 points, $P < .0001$). The microneedling group, in comparison with the fractional CO_2 laser group, also had a greater reduction in acne scarring severity score from baseline to three months after the last session (mean difference 2.07 points, $P < .0001$). However, the pattern of change of acne scarring severity score did not differ significantly over time between the groups of "microneedling plus PRP" and "microneedling alone" (no group×time interaction, mean difference 0.16 points, $P = 0.80$).

Significant decreases were observed in the depth of the scars of all three groups three months after the last visit (Table 3). The microneedling plus PRP group, in comparison with the fractional CO_2 laser group, had a greater reduction in the depth of the scars from baseline to three months after the last session (mean difference 4.58 mm, $P < .0001$). Compared with the fractional CO_2 laser group, the microneedling group had a greater reduction in the depth of the scars from baseline to three months after the last session (mean difference 2.00 points, $P = 0.01$). Finally, an additional decrease was found in the depth of the scars of the microneedling plus PRP group compared with the microneedling group from baseline to three months after the last session (mean difference 2.58 mm, $P = 0.02$).

According to GEE analyses, age, gender, and acne duration were not significant predictors of change in acne scarring severity score ($P = 0.52$, $P = 0.20$, and $P = 0.84$, respectively).

There was a significant difference in median patient satisfaction scores of the study groups ($P = 0.04$). The median patient satisfaction score was 60% (IQR: 30% to 70%; range: 15% to 80%) in the microneedling plus PRP group, 40% (IQR: 20% to 60%; range: 10% to 80%) in microneedling group, and 50% (IQR: 40% to 60%; range: 30% to 80%) in the fractional CO_2 laser group. A significant difference was observed between the microneedling plus PRP group and the microneedling group in the median patient satisfaction scores ($P = 0.03$). Also, the median patient satisfaction scores differed significantly between the microneedling group and fractional CO_2 laser group ($P = 0.04$). However, the microneedling plus PRP group and fractional CO_2 laser group were similar in the median patient satisfaction scores ($P = 0.57$).

DISCUSSION

In this research, we investigated the effect of microneedling alone, microneedling plus PRP, and fractional CO_2 laser on improving acne scars. Our results revealed that a striking decline occurred in severity of acne scar after a three-month period of treatment. The level of improvement and patients' satisfaction in the microneedling plus PRP group were more than those of other groups. Also, this study assessed the severity and depth of acne scars by Goodman and Baron's quantitative grading and Visio Face systems, respectively

In the study conducted by Niwat *et al.* in 2009 [19], 31 patients were treated with microneedling; the results indicated an improvement of 50% in acne scars in 67.74% of patients. Also, in a research carried

out on 36 patients treated with microneedling, 34 cases showed a significant reduction in the severity of acne scars [20]. In 2014, Dogra *et al.* [1] performed five microneedling sessions monthly in 30 acne scars patients with skin types IV and V. The results of their research showed a relative improvement in all patients, consistent with the results of current research.

Based on most studies [4,11,13,21,22], fractional CO_2 laser improves acne scars in the mild to moderate range. However, based on some evidence, the improvement rate has been reported in the range of about 26 to 75% [23,24]. Some studies also have reported an average improvement of 83% [4,11]. In the current study, the severity of acne scars was reduced by about 50% three months after treatment in those patients treated with fractional CO_2 laser, consistent with the results of previous studies [13,21,22]. In agreement with other studies [13,21-24], post-inflammatory hyperpigmentation (PIH) was the major side effect in patients treated with fractional CO_2 laser.

In a study by Leheta *et al* [25], 39 patients were examined to show whether a mixed treatment method of the microneedling plus trichloroacetic acid 20%, fractional CO_2 laser, or both treatments with alternate sessions are effective for acne scars. Gawdat *et al.* [26] carried out studies using PRP and fractional CO_2 laser, and the results showed that the areas treated with a combination of PRP and fractional CO_2 laser had a markedly better response. Also, in a research conducted by Zhu *et al.* [10], the effectiveness of PRP was examined, and they found that the general clinical improvement in patients treated with PRP was significantly better than that in the control patients. Redaelli *et al.* [27] conducted a study on 23 patients for three months and concluded that PRP was a promising and safe method to rejuvenate the face and neck and reduce acne scars. In this study, in microneedling plus PRP-treated patients, three and two patients could not complete follow-up due to lymphadenopathy and anemia, respectively. However, in the microneedling group, all the patients completed the follow-up without any side effects.

In a case report, a 35-year-old woman underwent PRP with microneedling to stimulate new hair growth. The procedure was performed via a high-speed 12-needle device that traversed a depth of 2.2 mm into the skin. The patient came back in 24 hours complaining of severe pain in her posterior scalp and neck. Physical examination revealed large anterior and posterior cervical lymph nodes without any abscesses or signs of skin infection or damage [28]. Another study by Garg *et al.* showed that 2% of patients with atrophic acne scars who undergo treatment with the Dermaroller® (a drum-shaped, nonelectrical roller studded with 192 microneedles size of 1.5 mm) developed tender cervical lymphadenopathy that subsided after three weeks [29].

Fabbrocini *et al.* [30] indicated that PRP combined with microneedling was more effective than microneedling alone in improving acne scars. They also showed that the depth of the acne scar after three months of treatment significantly decreased from about 12 mm to 9.7 mm. Similar to our study, as observed in published papers [11,23,27], Majid *et al.* evaluated the effectiveness of fractional CO_2 laser with the Dermaroller in the treatment of atrophic facial scars with various symptoms. They reported an excellent response in 72.2% of patients, good response in 16.7% of patients, and no improvement in 11.1% of the patients [4]. Similar results were also reported in the study conducted by Alam *et al.* [31]. They examined the effect of PRP in 40 patients with atrophic acne scars and found a moderate level of satisfaction (70%) among patients and physicians during the six months after surgery.

In this paper, given the 60% satisfaction in patients treated with microneedling plus PRP group, significant improvement was seen after applying both treatment methods compared with patients of microneedling and fractional CO_2 laser groups. Fernandes *et al.* [32] showed that PRP was effective in improving skin scars, especially of the epidermis type. They also stated that this effect leads to more collagen production by stimulating the skin.

Nofal *et al.* [33] conducted a study on 45 patients with acne scars. They divided the patients into three equal groups. The first group received a subcutaneous injection of PRP, the second group received trichloroacetic acid 100% using chemical reconstruction technique of acne scar, and the third group was treated with a combination of skin needling with topical PRP. After treatment, there was outstanding healing in the three studied groups regarding the degree of acne scar, with no undesirable consequences. The three modalities

were statically effective and safe in atrophic acne scars treatment.

The authors of this trial have worked on the effect of needling for the treatment of various types of scars, especially acne scars [34-37], and have even worked on the applicability of needling for the management of acne itself [38], as well as its associations, sequels, and new therapeutic options [39-46]. We may need more research to achieve better control and therapy. On the other hand, PRP and laser [47-48] are the other fields of interest of the authors of this study; here, we tried to design a novel trial bringing these items together for acne scar management.

CONCLUSION

The results of this research revealed that microneedling is effective in improving acne scars alone or in combination with PRP. Considering the fewer side effects and acceptable cost-benefit profile of microneedling compared to PRP plus microneedling or fractional CO_2 laser, it could be considered the first choice for treating acne scars. This study shows that microneedling has fewer side effects and lower cost, making it more suitable to use than PRP or fractional CO_2 lasers. It seems that the combination of microneedling with other therapeutic methods may not have statistically significant higher improvement than using it alone. We recommend that further clinical trial studies be carried out with larger sample sizes and different skin types.

Acknowledgment

We gratefully acknowledge the technical and editorial support from Rasool Akram Medical Complex Clinical Research Development Center for helping us with this project.

Conflict of interest: None declared.

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