

Efficacy of autologous platelet-rich plasma combined with fractional ablative carbon dioxide resurfacing laser in treatment of facial atrophic acne scars: A split-face randomized clinical trial

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ABSTRACT

Background: Autologous platelet-rich plasma has recently attracted significant attention throughout the medical field for its wound-healing ability. **Aims:** This study was conducted to investigate the potential of platelet-rich plasma combined with fractional laser therapy in the treatment of acne scarring. **Methods:** Sixteen patients (12 women and 4 men) who underwent split-face therapy were analyzed in this study. They received ablative fractional carbon dioxide laser combined with intradermal platelet-rich plasma treatment on one half of their face and ablative fractional carbon dioxide laser with intradermal normal saline on the other half. The injections were administered immediately after laser therapy. The treatment sessions were repeated after an interval of one month. The clinical response was assessed based on patient satisfaction and the objective evaluation of serial photographs by two blinded dermatologists at baseline, 1 month after the first treatment session and 4 months after the second. The adverse effects including erythema and edema were scored by participants on days 0, 2, 4, 6, 8, 15 and 30 after each session. **Results:** Overall clinical improvement of acne scars was higher on the platelet-rich plasma-fractional carbon dioxide laser treated side but the difference was not statistically significant either 1 month after the first treatment session ($P = 0.15$) or 4 months after the second ($P = 0.23$). In addition, adverse effects (erythema and edema) on the platelet-rich plasma-fractional carbon dioxide laser-treated side were more severe and of longer duration. **Limitations:** Small sample size, absence of all skin phototypes within the study group and lack of objective methods for the evaluation of response to treatment and adverse effects were the limitations. **Conclusion:** This study demonstrated that adding platelet-rich plasma to fractional carbon dioxide laser treatment did not produce any statistically significant synergistic effects and also resulted in more severe side effects and longer downtime.

Key words: Acne, fractional carbon dioxide laser resurfacing, laser ablation, platelet-rich plasma, scar

INTRODUCTION

Facial scarring caused by severe acne in adolescence and early adulthood is a common cosmetic problem accompanied by considerable psychological distress.

The main cause of scarring is the formation of compromised collagen occurring during the natural wound-healing process. Different procedures have

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been used to influence dermal remodeling including surgical techniques (subcision, punch graft and punch excision), resurfacing techniques (dermabrasion, chemical peel, traditional ablative and non-ablative laser treatment) and tissue augmentation agents (autologous fat transfer and injection of dermal fillers).^[1] In spite of these, treatment of acne scarring remains a challenge.

Facial resurfacing with fractional lasers is currently accepted to be one of the most effective treatments for facial scars.^[2] Ablative fractional carbon dioxide lasers generate thermal energy targeting the separated columns of skin at specific depths called the microthermal treatment zones.^[3,4] This method intrinsically spares the tissue around the treated columns from damage allowing for prompt epidermal regeneration of the treated zones.^[5] In addition, the enormous heat generated during ablative fractional carbon dioxide laser treatment can remove dermal tissue and bring about tissue shrinkage in the adjacent dermal collagen accompanied by collagen remodeling and skin tightening.^[6]

Regardless of the profound effect of fractional carbon dioxide lasers in the treatment of acne scars, there are still some major concerns restricting the widespread use of this procedure.^[7-11] These limitations include the risk of post-inflammatory hyperpigmentation, scarring and the longer post-procedure down time required that can disrupt patients' daily lives.

Autologous platelet-rich plasma contains the plasma portion of autologously sourced blood with an iatrogenically high platelet concentration.^[12] Recently, platelet-rich plasma has become popular in many areas of medicine including plastic surgery and dermatology for scar remodelling.^[13-17] Platelets release growth factors including platelet-derived growth factor and transforming growth factor- β , facilitating and accelerating bone and soft tissue regeneration.^[18-21] We hypothesized that given its regenerative properties, platelet-rich plasma may augment the response of acne scars to fractional carbon dioxide laser treatment and minimize the post-procedure side effects. This study aimed to investigate the potential of the combination therapy with autologous platelet-rich plasma and fractional carbon dioxide laser in enhancing the treatment response of facial acne scars and reducing the risk of adverse events.

METHODS

Patients

A total of 16 patients (12 women, 4 men), aged 22–52 years (mean age: 36.8), of Fitzpatrick skin types II–IV with moderate to severe facial atrophic acne scars (predominantly rolling and boxcar types with fewer than 20% of the icepick type) were enrolled in this study. We used the grading system suggested by Goodman and Baron for qualitative grading of the participants' acne scars.^[22] Those with a history of keloid formation, herpes simplex infection, any active inflammation, diabetes mellitus, collagen vascular disease, oral isotretinoin use within the previous 6 months, pregnancy, lactation and ablative or non-ablative laser skin resurfacing in the previous 12 months were excluded. This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of Isfahan University of Medical Sciences. Written informed consent was obtained from all the participants. The study was registered at the Iranian Registry of Clinical Trials; www.irct.ir, registration number: IRCT2014080218648N1.

Platelet-rich plasma preparation

A two-stage centrifuging process was employed in the preparation of platelet-rich plasma. Whole blood samples (20 ml) were drawn from the participant's medial cubital vein in a syringe and transferred to a tube prefilled with 2.4 ml anticoagulant (citrate phosphate dextrose) solution. The mixture was then centrifuged at 2000 g for 3 min. After the first spin, the lower red blood cell portion was discarded and the supernatant that contained platelet-poor plasma and buffy coat was centrifuged at 5000 g for 5 min. The resulting pellet of platelets (lower portion) was mixed with 4 ml of supernatant. This process produced approximately 4 ml of platelet-rich plasma. Three percent calcium chloride was added as platelet activator.

Treatment procedure

About 60 min before the starting the treatment, the targeted region was treated with topical anesthetic cream (mixture of lidocaine 2.5% and prilocaine 2.5%, Xyla P [Tehran Chemical Pharmaceutical Co., Tehran, Iran]) and icepacks to alleviate the pain followed by gentle cleansing and application of 70% isopropyl alcohol as disinfectant.

Subsequently, the dermatologist (ShK) treated both the cheeks of each participant using the ablative carbon

dioxide fractional laser (Q-ray, Diosis Inc., Seoul, Korea). In each treatment session, these parameters were used: laser power, 25; dot cycle (duration), 3; energy, 30mj, pixel pitch, 1 and ablation depth, 600 μm .

After the ablative carbon dioxide laser resurfacing treatment, each patient was administered autologous platelet-rich plasma on one half of the face (selected randomly) and normal saline was administered on the other half. Injection sites were located within 2 cm intervals to receive 0.2 ml platelet-rich plasma or normal saline. Afterwards, the participants were required to compress their faces with gauze for 15 min before leaving. Ice packs or analgesic medications were not used after treatment. All patients were asked to avoid direct sun exposure, heat and friction on the treated areas. They were instructed to apply a topical antibiotic (mupirocin) cream twice daily for 5 days after the treatment session and a broad spectrum sunscreen with a sun protection factor (SPF) of at least 30 every morning. One month after the initial treatment session, all participants received the second treatment session with the same protocol.

Patient assessment

Participants were required to undergo serial photography of the lesions at baseline, 1 month after the first treatment session and 4 months after the second, using a digital camera (Visio Face[®] 1000, >12 megapixels, CK Electronic Inc., Germany). Camera setting, lighting and positioning were kept identical for all serial photographs. A quartile grading scale: poor, <25% improvement; fair, 25–50% improvement; good, 51–75% improvement and excellent, >75% improvement was used by two blinded dermatologists (GF and ShB who did not perform the procedures) to evaluate the overall clinical improvement.

Each participant was instructed to evaluate his/her overall satisfaction with the treatment 1 month after the first treatment session and 4 months after the last, using a quartile grading system which defines 0 as unsatisfied, 1 as slightly satisfied, 2 as satisfied, or 3 as very satisfied. The visual analog scale (scoring from 0 to 10) was used to record adverse events (erythema and edema) as perceived by participants on days 0, 2, 4, 6, 8, 15 and 30 after each treatment session. Finally, the occurrence of other possible side adverse

events including secondary infection, acneiform eruption, dyschromia and new scar formation was assessed by a blinded dermatologist.

Statistical analysis

SPSS version 20 for Microsoft Windows was used for statistical analysis (SPSS Inc., Chicago, IL, USA). The Wilcoxon rank test was used to compare the results of the two methods for the degree of clinical improvement of acne scars and patient satisfaction. The paired *t*-test was utilized for group comparison of numerical variables (erythema and edema scores). $P < 0.05$ was considered statistically significant.

RESULTS

A total of 16 participants completed the study. Patient characteristics are shown in Table 1. Table 2 shows the acne scar grades of the two facial halves of the patients.

Dermatologist's evaluation

A quartile grading scale was used by two blinded dermatologists to assess the three serial photographs. A fair or good improvement was noted in 11 (68.8%) patients on the fractional carbon dioxide laser - platelet-rich plasma side and in 8 (50%) patients on the fractional carbon dioxide laser-normal saline side after the first treatment session ($P = 0.15$) [Figure 1]. Four months after the second session, there was a fair or good response in 14 (87.5%) patients on the fractional carbon dioxide

Table 1: Summary of participants' characteristics

Characteristics	Number
Age, range, mean	(22-52) 36.8
Sex (%)	
Women	12 (75)
Men	4 (25)
Fitzpatrick skin phototype (%)	
II	1 (6.2)
III	4 (25)
IV	11 (68.8)

Table 2: Frequency of acne scar grading in two groups

Acne scar severity	Facial halves	
	FCL + PRP	FCL + control
2	0	1
3	8	9
4	8	6
Total	16	16

PRP: Platelet-rich plasma, FCL: Fractional carbon dioxide

laser-platelet-rich plasma side and in 11 (68.8%) patients on the fractional carbon dioxide laser-normal saline side ($P = 0.23$) with none having an excellent outcome [Figure 2]. Figure 3 shows the serial figures of one patient.

Patient satisfaction

Eight (50%) patients stated that they were satisfied or very satisfied on the fractional carbon dioxide laser-platelet-rich plasma side, while five (31.2%) patients stated this about the fractional carbon dioxide laser-normal saline side 1 month after the first treatment session ($P = 0.18$) [Figure 4]. In addition, 4 months after the second treatment session, nine patients (56.2%) reported being satisfied or very satisfied on the fractional carbon dioxide laser-platelet-rich plasma side while seven patients (43.8%) described the same result on the fractional carbon dioxide laser-control side ($P = 0.12$) [Figure 5].

The fractional carbon dioxide laser-platelet-rich plasma side was found to have a better response than the fractional carbon dioxide laser-control side and participants were more satisfied with the fractional carbon dioxide laser-platelet-rich plasma side than the fractional carbon dioxide laser-control side; however, the difference was not found to be statistically significant.

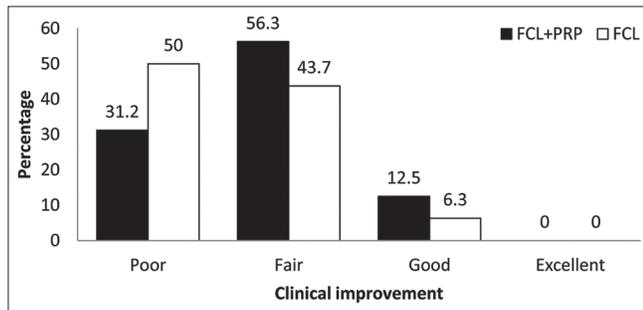


Figure 1: Dermatologists-assessed percentage of clinical improvement 1 month after the first treatment session

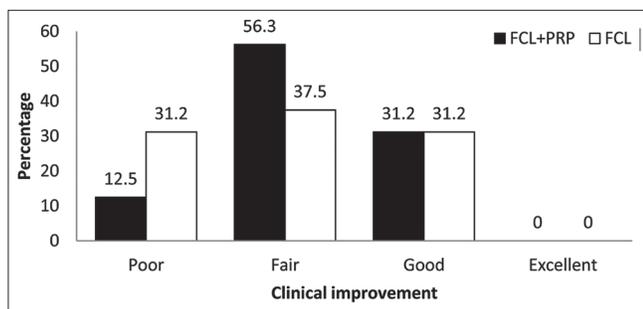


Figure 2: Dermatologists-assessed percentage of clinical improvement 4 months after the second treatment session

Side effects

Participants recorded the severity of erythema and edema on a 0–10 visual analogue score on days 0, 2, 4, 6, 8, 10, 15, 30 after each treatment session. Paired *t*-tests revealed more severe erythema on the fractional carbon dioxide laser-platelet-rich plasma side than the fractional carbon dioxide laser-control side with significant statistical difference on days 0, 2 and 4 ($P = 0.003$, $P = 0.007$, $P = 0.03$, respectively), as shown in Figure 6 (these results are of mean values from first and second treatments). Paired *t*-tests also revealed more severe edema on the fractional carbon dioxide laser-platelet-rich plasma side compared with

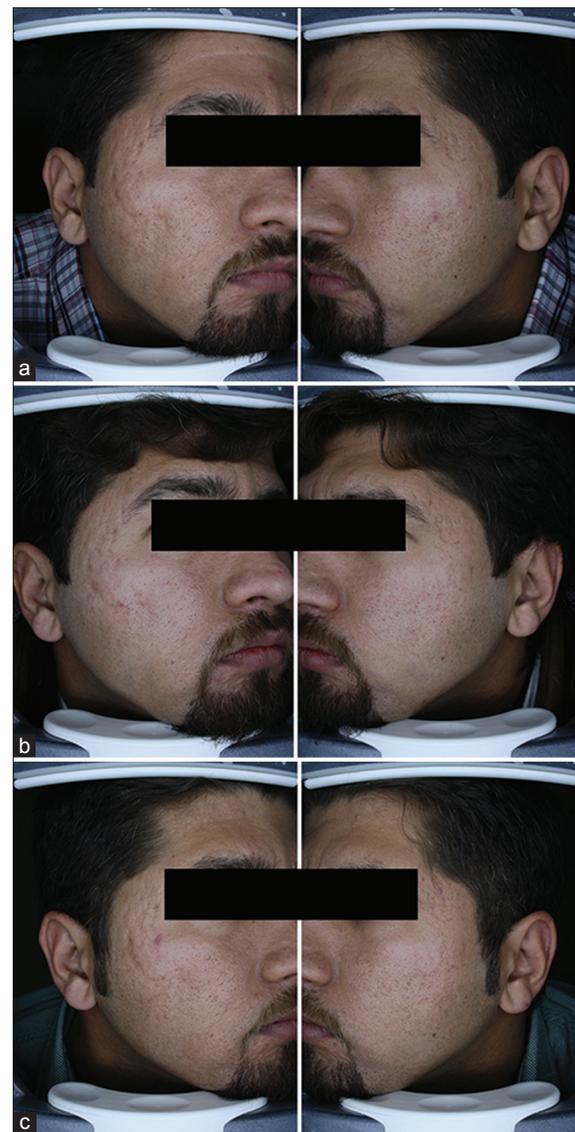


Figure 3: Left side of picture: Platelet-rich plasma - fractional carbon dioxide side, right side of picture: Fractional carbon dioxide-alone side (a) baseline, severe acne scar (b) 1 month after first treatment session, left side was scored poor and right side fair and (c) 4 months after second treatment session. Left side improved to good score but right side was again scored fair

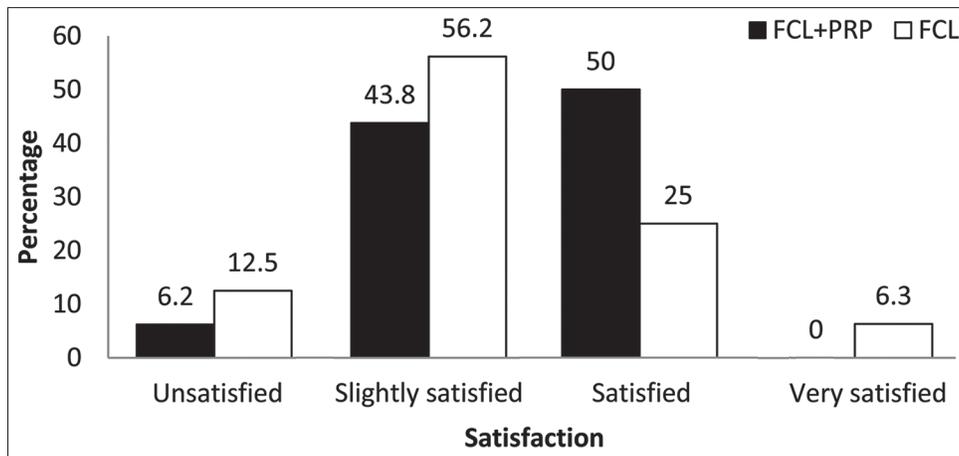


Figure 4: Percentage of patients' satisfaction 1 month after first treatment session

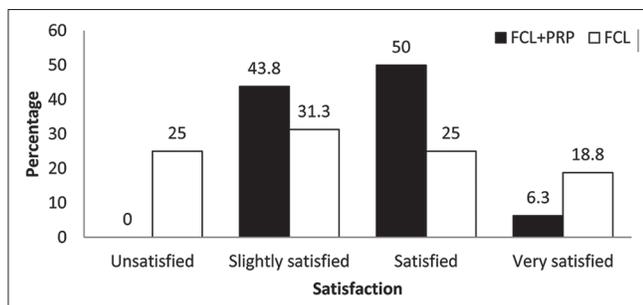


Figure 5: Percentage of patients' satisfaction 4 months after second treatment session

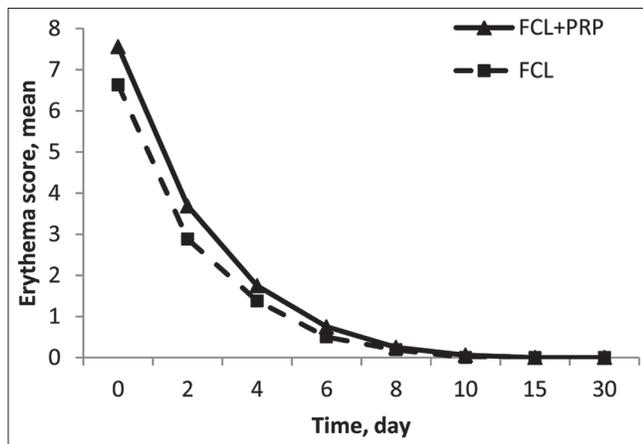


Figure 6: Patients-assessed mean score of erythema in two groups (these results are of mean values from first and second treatment sessions)

the fractional carbon dioxide laser-control side with a statistically significant difference on days 0, 2 and 8 ($P = 0.003, P = 0.004, P = 0.004$ respectively), as shown in Figure 7 (these results are of mean values from first and second treatments). The calculated mean duration of edema was about 6.3 ± 2.6 days on fractional carbon dioxide laser-platelet-rich plasma side and 5.1 ± 1.5 on fractional carbon dioxide laser-normal

saline side ($P = 0.12$). In addition, erythema lasted an average of 4.9 ± 3.1 days on the fractional carbon dioxide laser-platelet-rich plasma side and 4.1 ± 2.9 on fractional carbon dioxide laser-normal saline side ($P = 0.06$) indicating longer duration of edema and erythema on the fractional carbon dioxide laser-platelet-rich plasma side even when there is no significant statistical difference in severity. There were no reports of other adverse events including secondary infection, acneiform eruption, dyschromia and new scar formation.

DISCUSSION

Our results show that the combination of platelet-rich plasma and ablative fractional carbon dioxide lasers improved facial acne scars and resulted in greater patient satisfaction but not to a statistically significant level. Our study also showed that the adverse effects (erythema and edema) lasted longer and were more severe on the platelet-rich plasma-fractional carbon dioxide laser side when compared to the fractional carbon dioxide laser-normal saline side.

Recently, a few studies have looked into the effectiveness of platelet-rich plasma combined with ablative fractional carbon dioxide laser in the treatment of atrophic acne scars with most of them reporting that platelet-rich plasma caused greater clinical improvement and also reduced the laser side effects, erythema and edema. Lee *et al.* conducted a split-face trial on 14 Korean patients with facial atrophic acne scars who were treated with platelet-rich plasma following ablative fractional carbon dioxide laser. Patients received ablative fractional carbon dioxide laser on both sides of

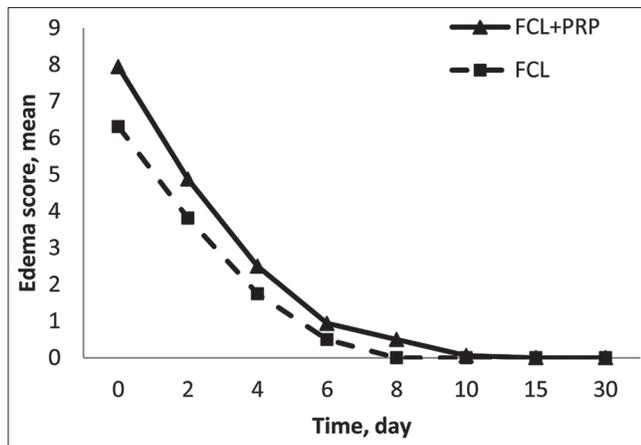


Figure 7: Patients-assessed mean score of edema in two groups (these results are of mean values from first and second treatment sessions)

the face and subsequently, they randomly received intradermal platelet-rich plasma on one half of the face and intradermal normal saline on the other half. Overall clinical improvement was significantly enhanced on the intradermal platelet-rich plasma-side than the other side. In contrast to our study, they reported that erythema and edema on the intradermal platelet-rich plasma-side improved faster. In their study, these two side effects were evaluated by blinded dermatologists and also by an objective method using a chromometer to evaluate the intensity of erythema.^[13]

The correlation between shorter down time and platelet-rich plasma following fractional carbon dioxide laser was demonstrated in another study as well. Gawdat *et al.* used topical and intradermal platelet-rich plasma after ablative fractional carbon dioxide laser for acne scar treatment in 30 patients. One group underwent treatment with fractional carbon dioxide laser-intradermal platelet-rich plasma on one side and fractional carbon dioxide laser-intradermal normal saline on the other side. The other group underwent fractional carbon dioxide laser with intradermal platelet-rich plasma on one side and fractional carbon dioxide laser with topical platelet-rich plasma on the other side. In addition to reporting synergistic effects on clinical response and patient satisfaction after adding platelet-rich plasma to fractional carbon dioxide laser, they also showed that side effects were fewer on the platelet-rich plasma sides (both intradermal and topical) than the other sides.^[15] Other studies also reported less erythema after adding platelet-rich plasma to laser therapy.^[23,24]

There are several mechanisms that could explain the synergistic effects of platelet-rich plasma on overall clinical improvement. Activated platelets possess α -granules containing secretory proteins (e.g., platelet-derived growth factor and transforming growth factor). These proteins are bound to the receptors of target cells (e.g., mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells and epidermal cells) and direct cellular proliferation, matrix formation, osteoid production, collagen synthesis, etc.^[25,26] Platelet-derived growth factor, transforming growth factor- β and IGF also facilitate chemotaxis and mitogenesis of stem cells and osteoblasts, angiogenesis for capillary ingrowth, bone matrix formation and collagen synthesis.^[27-29]

Another mechanism is the production of hyaluronic acid which can absorb water resulting in volume and skin turgor, stimulation of cell proliferation, extracellular matrix production and modulation of the diameter of collagen fibers.^[24]

Our results show that although platelet-rich plasma can have a role in the treatment of atrophic acne scars, it has more local side effects. This worsening of erythema and edema could be attributed to the accumulating evidence that demonstrates that platelets contribute to the initiation and propagation of the inflammatory process.^[30]

Study limitations

The limitations of our study include small sample size, absence of all skin phototypes and the lack of objective methods for clinical evaluation of acne scar improvement and side effects. We feel that further studies are required to investigate the mechanism, benefits and safety of autologous blood-derived platelet-rich plasma.

CONCLUSION

Adding platelet-rich plasma to ablative fractional carbon dioxide laser resulted in non-significant synergistic effects with more severe side effects and longer downtime.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to

be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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