

# The Efficacy of Autologous Platelet Rich Plasma Combined with Ablative Carbon Dioxide Fractional Resurfacing for Acne Scars: A Simultaneous Split-Face Trial

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**BACKGROUND** Ablative carbon dioxide (CO<sub>2</sub>) fractional resurfacing is a promising therapeutic intervention for the treatment of acne scars, although this technique is associated with prolonged surgical site erythema and edema, which may affect the daily lives of patients. Autologous platelet-rich plasma (PRP) is known to enhance wound healing and has applications in many areas of medicine.

**OBJECTIVES** To evaluate the synergistic effects of autologous PRP with CO<sub>2</sub> fractional resurfacing for acne scars.

**MATERIALS AND METHODS** A split-face trial was conducted in 14 Korean participants with acne scars. All participants received one session of ablative CO<sub>2</sub> fractional resurfacing. Immediately after resurfacing, facial halves were randomly assigned to receive treatment with autologous PRP injections on one side (experimental side) and normal saline injections on the other side (control side). The participants were monitored for degree of recovery and resurfacing-associated adverse events, including prolonged erythema, edema, and other effects on days 0, 2, 4, 6, 8, 15, and 30. The intensity of erythema was objectively measured using a chromometer at the same time intervals. After one additional treatment session using the same protocol, two independent dermatologists evaluated clinical improvement using a quartile grading scale.

**RESULTS** All participants completed the study. Erythema on the experimental side improved faster than on the control side and was significantly less at day 4 ( $p = .01$ ). This difference was confirmed using a chromometer ( $p = .049$ ). Total duration of erythema was an average of  $10.4 \pm 2.7$  days on the control side and  $8.6 \pm 2.0$  days on the experimental side ( $p = .047$ ). Edema also improved faster on the experimental side than on the control side. The total duration of edema was an average of  $7.1 \pm 1.5$  days on the control side and  $6.1 \pm 1.1$  days on the experimental side ( $p = .04$ ). Participants were also assessed for duration of post-treatment crusting, with a mean of  $6.8 \pm 1.0$  days on the control side and  $5.9 \pm 1.1$  days on the experimental side ( $p = .04$ ). No other adverse effects were observed in any participant. Four months after the final treatment, overall degree of clinical improvement was significantly better on the experimental side ( $2.7 \pm 0.7$ ) than on the control side ( $2.3 \pm 0.5$ ) ( $p = .03$ ).

**CONCLUSIONS** Treatment with PRP after ablative CO<sub>2</sub> fractional resurfacing enhances recovery of laser-damaged skin and synergistically improves the clinical appearance of acne scarring.

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Fractional ablative carbon dioxide (CO<sub>2</sub>) lasers produce discrete columns of thermal damage at specific depths, referred to as microthermal treatment zones (MTZs). This technique characteristically spares the tissue surrounding each column, ultimately resulting in rapid epidermal regeneration. Mechanistically, this is believed to derive from the fast migration of viable keratinocytes present at the peripheral wound edges. Consequently, treatment

with fractional CO<sub>2</sub> lasers minimizes patient downtime and post-treatment complications associated with traditional ablative laser resurfacing. Nonetheless, this modality is still associated with a long period of erythema and edema (~5–10 days), which may hinder patients' daily lives.<sup>1</sup> Fractional CO<sub>2</sub> lasers are employed for the treatment of acne scarring, photoaging, and skin laxity, as well as for various other indications.

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Autologous platelet-rich plasma (PRP) can enhance wound healing, which has been demonstrated in controlled animal studies for soft and hard tissues.<sup>2,3</sup> The application of autologous PRP to surgical wounds has been shown to accelerate tissue repair and reduce postoperative pain.<sup>4</sup> Recently, the efficacy and safety of autologous PRP treatment has been reported in many areas of medicine, including orthopedics, sports medicine, dentistry, otorhinolaryngology, neurosurgery, ophthalmology, urology, wound healing, and cosmetic and maxillofacial surgery,<sup>5–18</sup> but many of these reports are anecdotal, and few include controls to objectively determine the role of PRP. We hypothesized that intradermal injection of autologous PRP after ablative CO<sub>2</sub> fractional resurfacing would accelerate tissue repair and reduce adverse effects such as prolonged erythema and edema. Herein, we evaluate the synergistic effects of treatment with autologous PRP after ablative CO<sub>2</sub> fractional resurfacing. We also assess whether this investigational treatment results in better overall clinical improvement than ablative CO<sub>2</sub> fractional resurfacing alone.

## Materials and Methods

### Participant Selection

Fourteen Korean participants (Fitzpatrick skin types III–V) with moderate to severe acne scars were enrolled in this study. The mean participant age was 28.1 (range 21–38), and the sample included four women and 10 men (Table 1). Participants were excluded if they reported a history of keloid scar formation, any active inflammation, oral isotretinoin use within the preceding 6 months, diabetes, colla-

gen vascular disease, or ablative or nonablative laser skin resurfacing within the preceding 12 months, or were pregnant or lactating.

### PRP Preparation

PRP was produced using a commercially available two-part system (Prosys PRP, T·Cell Bio Inc., Seoul, South Korea) consisting of a disposable separation kit and a concentration kit. First, anticoagulant was aliquotted using a 20-mL syringe at a ratio of 1:10 (anticoagulant/blood); 60 mL of blood was then drawn from the participant's medial cubital vein. To ensure adequate mixing, the blood was aliquotted into the anticoagulant over a period of 10 seconds. The anticoagulated blood was then gently pipetted into the separation kit to minimize red blood cell damage. The mixture was then centrifuged at a speed of 3,000 rpm for 3 minutes. The blood was separated into platelet-poor plasma (PPP), buffy coat, and red blood cells. Because PRP is a mixture of buffy coat and plasma, red blood cells were extracted from the kit. For further concentration, the separated fraction composed of PPP and buffy coat was centrifuged with the concentration kit for 3 minutes at 4,000 rpm. Concentrated PRP was then withdrawn. This process produced approximately 6 mL of PRP for each participant.

### Treatment Protocol

Before treatment, all treatment areas were gently cleansed using a mild cleanser, and a topical anesthetic cream (EMLA, AstraZeneca, Wilmington, DE) was applied for 30 minutes. Each participant's entire face was then treated with an ablative CO<sub>2</sub> fractional laser (Q-ray, Diosis Inc., Seoul, Korea). Each

**TABLE 1. Summary of Subject Demographics**

Sex	N	Age, Range (Mean)	Fitzpatrick Skin Type					
			I	II	III	IV	V	VI
Female	4	25–32 (28.0)	—	—	1	2	1	—
Male	10	21–38 (28.1)	—	—	2	5	3	—
Total	14	21–38 (28.1)	—	—	3	7	4	—

treatment session used a pulse energy of 25 mJ per fixed 150- $\mu\text{m}$ -diameter microbeam and a density of 400 MTZ/cm<sup>2</sup>. Concurrent forced-air cooling was used for epidermal protection. After ablative CO<sub>2</sub> laser resurfacing, facial halves were randomly assigned to receive treatment with autologous PRP on one side and normal saline on the other. Participants underwent intradermal autologous PRP or normal saline injections under sterile conditions at 20 individual sites on the each side of the face. Sites were spaced at 1.5- to 2-cm intervals, and each site received 0.3 mL of PRP or normal saline. Participants were then instructed to compress their faces with gauze for 15 to 20 minutes while remaining supine before being discharged to go home. All participants with a history of herpes labialis were prophylactically treated with oral famciclovir 500 mg daily for 5 days after treatment. One month after the initial treatment, all participants underwent one additional treatment session with the same therapeutic protocol.

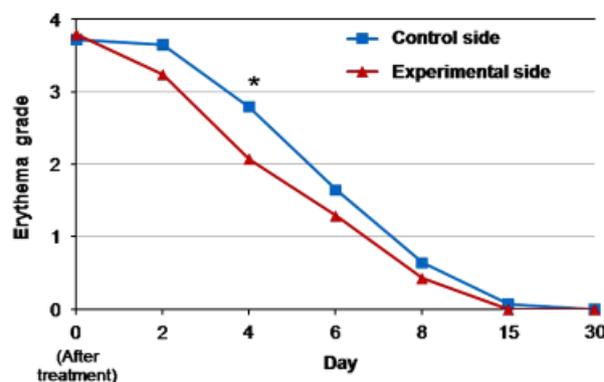
### Evaluation Criteria

Each participant was photographed twice, once at baseline and once 4 months after the last treatment session (Canon EOS 40D, 10.0 megapixels, Tokyo, Japan). Participants were photographed in the same position both times, with identical camera settings and lighting and by the same photographer. After the first treatment session, participants were evaluated for adverse events at days 0, 2, 4, 6, 8, 15, and 30. Erythema and edema were graded on a 5-point scale (0 = none, 1 = trace, 2 = mild, 3 = moderate, 4 = severe). A blinded dermatologist assessed other side effects (petechiae, oozing, crusting, dyschromia, and scarring) as present or absent. Participants also documented the duration of any treatment-associated symptoms during their recovery. To objectively assess erythema intensity, all participants were evaluated using a skin color measuring device (Chromameter CR-400, Minolta Co., Tokyo, Japan) on 15 regions of normal skin on both cheeks at the same time intervals and median values were selected and recorded by investigator. This system measures spectrometric

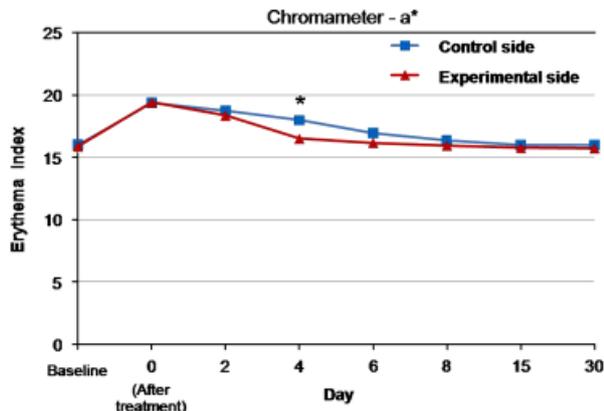
reflectance data and allows colors to be quantified according to three axes ( $L^*a^*b^*$  system): white-black or lightness ( $L^*$ ), red-green or chrome ( $a^*$ ), and yellow-blue or hue ( $b^*$ ).  $L^*$  represents lightness;  $a^*$ , redness or greenness; and  $b^*$ , yellowness or blueness. Two different blinded dermatologists evaluated overall clinical improvement, comparing digital photographs taken before treatment (baseline) and 4 months after the last treatment using a quartile grading scale (0, no improvement; 1, <25% improvement; 2, 25–50% improvement; 3, 51–75% improvement; and 4, >75% improvement). All data obtained were evaluated using t-tests, and  $p < .05$  was considered statistically significant.

### Results

All 14 participants completed the study. According to physician evaluation, the resurfacing-associated erythema on the experimental side improved faster than the control side. The resurfacing-associated erythema on the experimental side was significantly less than on the control side at post-treatment day 4 ( $p = .01$ ). The variances in mean grades of post-treatment erythema are summarized in Figure 1. The differences in erythema were also confirmed using the chromometer, with statistically significant variances occurring on day 4 ( $p = .049$ ), as demonstrated

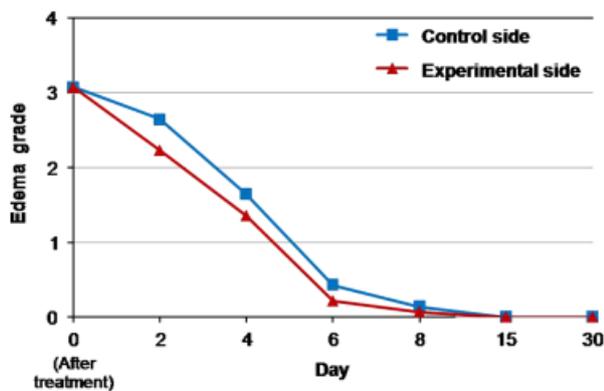


**Figure 1.** Variation in physician-assessed mean degree of erythema. The experimental side improved faster than the control side. \*Differences between the experimental side and control side were observed to be statistically significant at postoperative day 4 ( $p = .01$ ).



**Figure 2.** Variation in mean chromometer-rated erythema. The experimental side improved faster than the control side. \*Differences between the experimental and control side were statistically significant at postoperative day 4 ( $p = .049$ ).

in Figure 2. Total duration of erythema lasted an average of  $10.4 \pm 2.7$  days on the control side and  $8.6 \pm 2.0$  days on the experimental side ( $p = .047$ ). With regard to physician-assessed degree of post-treatment edema, the experimental side also improved faster than the control side, although the difference was not statistically significant. Data for the mean grade of post-treatment edema are summarized in Figure 3. Edema lasted an average of  $7.1 \pm 1.5$  days on the control side and  $6.1 \pm 1.1$  days on the experimental side ( $p = .04$ ). All participants were observed to experience some degree of post-treatment crusting, lasting an average of  $6.8 \pm 1.0$  days on the control side and  $5.9 \pm 1.1$



**Figure 3.** Variation in mean physician-assessed degree of edema. The experimental side improved faster than the control side, although the observed difference was not statistically significant.

days on the experimental side ( $p = .04$ ). None of the other adverse events (petechiae, oozing, dyschromia, infection, scarring, or blistering) occurred in any participant. Four months after the final treatment, the overall degree of clinical improvement was assessed to be  $2.7 \pm 0.7$  on the experimental side and  $2.3 \pm 0.5$  on the control side ( $p = .03$ ) (Figures 4 and 5).

## Discussion

Autologous PRP is the plasma portion of autologously sourced blood with an iatrogenically high platelet concentration.<sup>5</sup> Ferrari and colleagues first used it in 1987 after open heart surgery to avoid excessive transfusion with homologous blood products.<sup>19</sup> Many studies have suggested that PRP can reduce inflammation, postoperative blood loss, infection, and narcotic requirements, in addition to accelerating osteogenesis and wound and soft tissue healing. In areas of tissue damage, platelets are the first cells to arrive at the site and play an important role in mediating tissue repair through the release of growth factors from their  $\alpha$ -granules.<sup>5</sup> These  $\alpha$ -granules contain storage pools of numerous growth factors, including platelet-derived growth factor, transforming growth factor beta, vascular endothelial growth factor, insulin-like growth factor, fibroblast growth factor, epithelial growth factor, and keratinocyte growth factor, as well as many cytokines, chemokines, and resulting metabolites. Because PRP is, by definition, platelet rich, it contains correspondingly high levels of these autologous growth factors.<sup>18</sup>

During the four phases of the wound-healing process—hemostasis, inflammation, proliferation, and remodeling—platelet growth factors regulate a well-orchestrated and complex series of events involving cell-cell and cell-matrix interactions, ultimately resulting in the promotion of mesenchymal stem cell proliferation at the wound site.<sup>5</sup> Because the tissue damage from ablative CO<sub>2</sub> fractional laser resurfacing is histopathologically similar to that of many wounds, we hypothesized that post-treatment intradermal injections of autologous PRP would



**Figure 4.** A 27-year-old woman (A) before the first treatment on the experimental (right) side, (B) 4 months after the final treatment on the experimental side, (C) before the first treatment on the control (left) side, and (D) 4 months after the final treatment on the control side. Significant improvement was observed, and the experimental side achieved greater clinical improvement than the control side.

accelerate recovery and reduce adverse events such as erythema or edema. Therefore, our study was designed to evaluate possible therapeutic advantages of treatment with autologous PRP after ablative CO<sub>2</sub> fractional resurfacing in the treatment of acne scars. Ours is the first study that conclusively demonstrates the synergistic effects of autologous PRP after ablative CO<sub>2</sub> fractional resurfacing in the treatment of acne scarring.

Because of the prolonged postoperative facial erythema and edema associated with ablative CO<sub>2</sub> fractional resurfacing, patients are often hesitant to undergo this intervention. Here, subjective and objective data indicate that post-treatment erythema

improved faster on the side treated with autologous PRP, with a significant difference occurring at postoperative day 4. Adjuvant PRP treatment may rapidly decrease early severe erythema after ablative CO<sub>2</sub> fractional resurfacing, which can affect patients' daily lives immediately after treatment. For post-treatment edema, the side receiving PRP also showed faster recovery times, although the differences did not reach statistical significance. Total duration of erythema, edema, and crusting were statistically significantly shorter on the side receiving PRP treatment than on the control side. These results verify that adjuvant PRP treatment may help promote the recovery of laser-damaged skin and decrease downtime. We propose that the mechanism



**Figure 5.** A 29-year-old man (A) before the first treatment on the experimental (right) side, (B) 4 months after the final treatment on the experimental side, (C) before the first treatment on the control (left) side, and (D) 4 months after the final treatment on the control side. Significant improvement was observed, and the experimental side achieved greater clinical improvement than the control side.

of action for these observed effects may be the numerous growth factors present in PRP, as described above. Specifically, platelet-derived growth factor may help to stimulate the production of other growth factors important in tissue remodeling, promoting connective tissue healing by upregulating collagen and protein synthesis. Higher levels of transforming growth factor beta may also expedite tissue recovery through the upregulation of cellular migration and proliferation, as well as by directly stimulating cell replication and fibronectin binding interactions. Insulin-like growth factor may also assist in the proliferation and migration of fibroblasts

and increase collagen production. Although the effects of epithelial growth factor are limited to the basal layer of the epidermis, it also promotes cell differentiation and re-epithelialization.<sup>20</sup> These growth factors may enhance the recovery of laser-damaged skin and shorten the duration and degree of postoperative erythema, edema, and crusting.

Independent physician assessments also rated the sides of the face that received postresurfacing autologous PRP treatment as showing greater overall clinical improvement. The mechanism of action for these observed effects may also be due to the

numerous growth factors present in PRP, as mentioned above. The numerous growth factors and triggered healing process may further promote the formation of new collagen fibers, providing long-term skin remodeling. Intradermal injection alone results in the dissolution of the binding connections between the papillary skin and deeper tissues and creates controlled trauma that leads to additional wound healing, like subcision.<sup>21</sup> By injecting normal saline on the control side, we avoided the therapeutic bias induced by intradermal injection alone. In our experiment, we provided two total injections and noted that one injection was not enough to provide a better overall clinical improvement. Thus, two or more combination treatments may be needed to achieve these results.

We did not compare the efficacy of intradermal PRP treatment with that of topical PRP treatment in this study. Theoretically, intradermal PRP has some advantages over topical PRP. Intradermal PRP components would penetrate the skin more easily and would probably exert a greater effect on laser-damaged skin, and as mentioned above, intradermal injection alone results in the dissolution of the binding connections between the papillary skin and deeper tissues and creates controlled trauma, which leads to additional wound healing, like subcision. And the cost of topical and intradermal PRP treatments is approximately the same. Therefore, when considering cost-effectiveness, intradermal treatment is likely to be superior to topical treatment.

In conclusion, our results show that PRP treatment after ablative CO<sub>2</sub> fractional resurfacing provides better overall clinical improvement and expedites the recovery of laser-damaged skin. We suggest that PRP should be considered as an adjuvant therapeutic option for aggressive dermatologic procedures such as ablative CO<sub>2</sub> fractional resurfacing. Two or three sessions of combination treatments should be suitable for patients who want to reduce downtime or for patients with recalcitrant moderate to severe acne, keeping in mind that PRP treatment is costly. This was a small pilot study, and additional controlled trials including studies with larger sets of

patients, patients with all skin types, and multiple treatment sessions, will be necessary to determine the true clinical benefit that this intervention offers.

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