

Patient Evaluation on Post Treatment Reactions of Fractional Ablative Carbon Dioxide Laser Combined with Autologous Concentrated Platelet Plasma

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ABSTRACT

Background: Growth factors can enhance wound repair, however, its role in post laser treatment is unclear. The aim of this study was to establish a more advantageous method to obtain autologous concentrated platelet plasma, which secretes growth factors, and to evaluate its benefits in the wound healing process, including skin reactions and adverse effects after carbon dioxide fractional resurfacing for acne scars.

Methods: A simultaneous split face trial was conducted in 31 patients with symmetrically atrophic acne scars on the face. Facial halves were randomly assigned to receive laser treatment with topical autologous platelet concentrated plasma (experimental side) or saline (control side). After treatment, participants recorded the degree and duration of recovery and side effects, including erythema, edema, pain, crusting, post inflammatory hyperpigmentation and folliculitis for duration of one month.

Results: Erythema reduction time and total duration was both faster on the experimental side, both ($p < 0.05$). Edema improvement time and total duration was similar, both ($p > 0.05$). Pain scores 12 hours post treatment were lower on the experimental side, ($p < 0.05$), but total duration of pain was the same. Initial time that crusting appears and starts to peel was faster on the experimental side, ($p < 0.05$) and ($p > 0.05$) respectively, but the time for the crust to peel completely was the same. On the control side, PIH was more severe, ($p < 0.05$), and appearance of folliculitis was more prevalent, ($p < 0.05$).

Conclusion: We established a simple and economically feasible method to obtain autologous concentrated platelet plasma, which patients evaluated could reduce erythema and pain, enhance wound healing, and reduce adverse effects such as PIH and folliculitis after laser treatment.

Keywords: Autologous concentrated platelet plasma; Fractional ablative carbon dioxide laser; Acne scars; Skin reactions after laser skin treatment; Adverse effects after laser skin treatment

INTRODUCTION

Fractional ablative carbon dioxide (CO_2) laser is a safe and currently the most effective treatment modality for acne scars. It creates an array of microscopic treatment zones (MTZ) of thermal injury to the skin, sparing surrounding tissues in the MTZ, allowing rapid epidermal regeneration within 24 hours of exposure [1], which expedites wound repair. There is evidence of a sustained long term efficacy by the detection of heat shock protein 70 as early as two days

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post treatment up to 3 months post treatment, and type III collagen in the dermal layer 7 days post treatment [2]. However, post treatment downtime and complications are still reasons why patients hesitate to receive such treatment. Different products and procedures to reduce these risks are a popular research subject these days.

Platelet rich plasma (PRP) is defined as “abundant platelets that are concentrated into a small volume of plasma [3]”, and platelets secrete fundamental growth factors [4] that can accelerate wound healing, and is used in many areas of medicine, including cosmetic surgery, plastic surgery, oral and maxillofacial surgery. However, little is known about the effects of PRP combined with laser treatment.

The traditional method of PRP extraction has potential risks [6], and tedious procedural steps. Companies have started selling PRP kits, and there are at least 16⁶ types of commercially available PRP extraction kits, but some of the products are very expensive. Using the basic principle of PRP preparation, the aim the present study was to establish a safe, effective, simplified, and economically feasible method to obtain autologous concentrated platelet plasma, and to observe if it could alleviate post laser treatment skin reaction, quicken wound healing time, and reduce adverse effects.

METHODS AND MATERIALS

Participant Selection

This study was conducted at the Peking University People's Hospital, Department of Dermatology. In total, thirty one participants (23 women, 8 men; age range 21-46 years; mean age 28.6 years; Fitzpatrick skin types III-IV) were enrolled in this study. Patients had moderate to severe symmetrically atrophic acne scars, and had no or few inflammatory papules and pustules on the face. Participants were excluded if they reported a history of keloid scar formation, hypertension or diabetes, treatment with oral isotretinoin within the preceding 6 months, immunosuppressive treatment or disorders, pregnant or lactating women, skin dermabrasion or other forms of skin resurfacing within the preceding 2 weeks. The study was approved by the ethical committee of the Peking University People's Hospital, and each participant provided written informed consent.

Autologous Concentrated Platelet Plasma Preparation

For the preparation of autologous platelet concentrated plasma, a slight modification of Choukroun's PRP method [7] was used. First, 10 mL of autologous whole blood was collected into a vacutainer collection tube with no additives and immediately centrifuged at 3000rpm for 10 minutes. Three layers appeared: from top to bottom are the plasma and serum, the buffy coat, and the red blood cells. The plasma and serum is removed by a syringe into a sterile glass tube with no additives. After the glass tube has been

immobile for 5 minutes at room temperature, a platelet clot will appear, and growth factors can be extracted after agitation by a syringe.

Treatment Protocol

Before treatment, participants cleansed their entire face using a mild cleanser. 60 to 90 minutes prior treatment, a topical anesthetic cream (5% Compound lidocaine cream 5g) was applied on the face and occluded with saran wrap, and participants were given analgesics (Ibuprofen 300mg, and Oxycodone and Acetaminophen Tablets 5mg/325mg). Each participant was treated with ablative CO₂ fractional laser (Acupulse, Lumenis, USA). Both deep and superficial treatment modalities were used. For the deep treatment mode, each region's pulse energy and density were set as follows: cheeks (15mJ/cm², 4%), forehead (12.5mJ/cm², 4%), and nose (17.5mJ/cm², 4%). For the superficial treatment mode: cheeks (60mJ/cm², 40%), forehead 50mJ/cm², 40%), and nose (70mJ/cm², 40%). After laser resurfacing, facial halves were randomly assigned to receive topical autologous platelet concentrated plasma (experimental group) or normal saline (control group). 1-1.5mL of plasma or saline were applied topically and occluded for 20 minutes. Participants were instructed not to apply any cosmetic products in the next 24 hours.

Evaluation Criteria

Participants monitored and recorded the degree and duration of recovery and side effects, including erythema, edema, pain, crusting, PIH and folliculitis for duration of one month. Duration and recovery of erythema, edema, pain, and crusting was graded on a 5-point scale (0= none, 1= trace, 2= mild, 3= moderate, 4= severe). PIH graded on a 3-point scale, (0= none, 1= detectable, 2= obvious). Folliculitis was noted either as present (1) or not (0).

Statistical Analyses

All data were analyzed using SPSS19 for Windows. Before-and-after treatment comparisons were performed using the parametric *t*-test for paired samples. Non-parametric data between the two sides were evaluated using the Wilcoxon and McNemar test. All data *p*<0.05 was considered statistically significant.

RESULTS

Subjective Evaluation

Skin Reactions

All 31 subjects completed the study. Erythema improved on day 1.9 ± 1.2 on the experimental side, and total duration of erythema was 7.8 ± 5.2 days. Erythema improved on day 2.6 ± 1.8 on the control side, and total duration of erythema was 9.0 ± 5.7 days. Erythema reduction time and total duration

was both faster on the experimental side (**Figure 1**), both ($p < 0.05$).

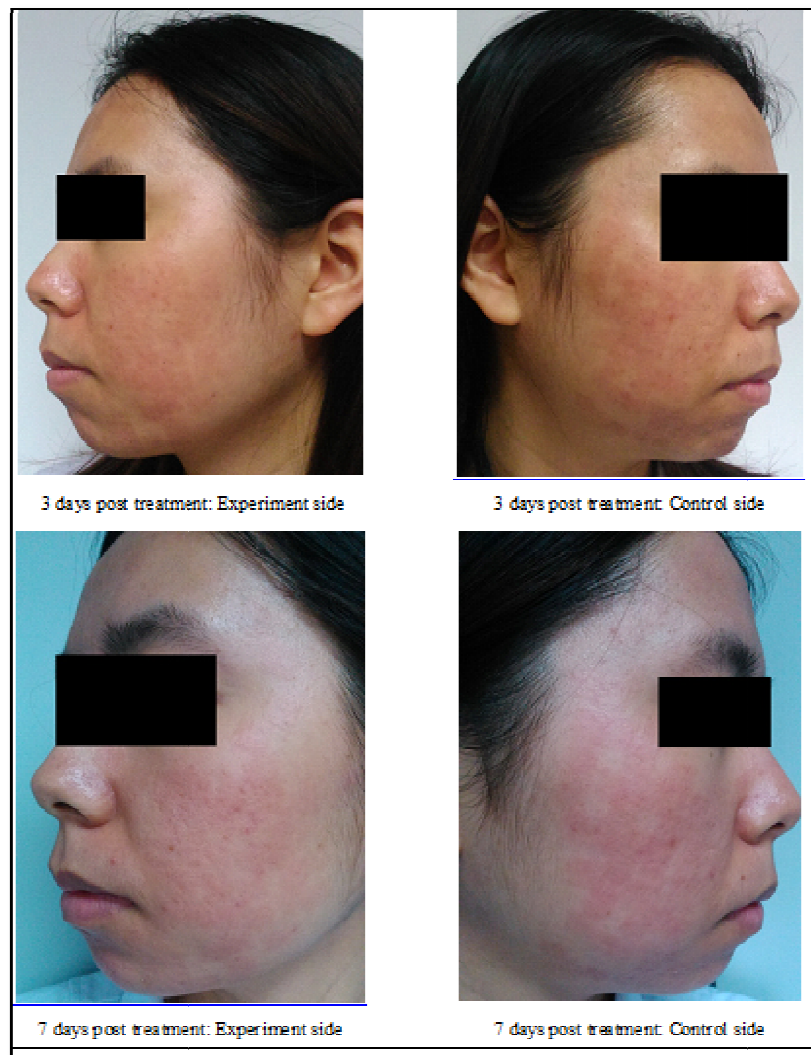


Figure 1. Erythema reduction

Edema improved on day 1.3 ± 0.7 on both sides, and lasted 2.7 ± 1.8 days on the experimental side, and 2.7 ± 1.9 on the control side (**Figure 2**), both ($p > 0.05$).

Pain score 12 hours post treatment on the experimental side was 1.5 ± 1.1 , and 1.7 ± 1.0 on the control side. Total duration of pain was the same on both sides, lasting 1.1 ± 1.3 days. Pain scores 12 hours post treatment were lower on the experimental side, ($p < 0.05$), but total duration of pain was the same on both sides, ($p > 0.05$).

Wound Repair

Initial crusting time on the experimental side was 1.3 ± 1.0 days, and 1.5 ± 1.1 on the control side, initial time crusting

starts to peel was 3.5 ± 2.0 days on the experimental side, and 3.6 ± 2.1 on the control side (**Figure 3**), and time it takes for the crust to peel completely on both sides was 7.5 ± 3.5 days. Initial time that crusting appears and initial time that the crust starts to peel was faster on the experimental side, ($p < 0.05$) and ($p > 0.05$) respectively, but the time it takes for the crust to peel completely was the same, ($p > 0.05$).

Adverse Effects

PIH was noted in 6 patients (19.4%), out of these 6 patients, 1 patient had Fitzpatrick skin phototype III, and 5 with

phototype IV. From the experimental group, 25 patients had PIH grade of 0, 6 patients with PIH grade of 1, and 0 with PIH grade of 2. From the control group, 25 patients had PIH

grade of 0, 1 patient with PIH grade of 1, and 5 with PIH grade of 2. The difference of PIH grade between the two groups was statistically significant (**Figure 4**), ($p < 0.05$).



Figure 2. 2 days post treatment

(Right side: control side; Left side: experiment side)



Figure 3. 4 days post treatment: Experiment side 4 days post treatment: Control side

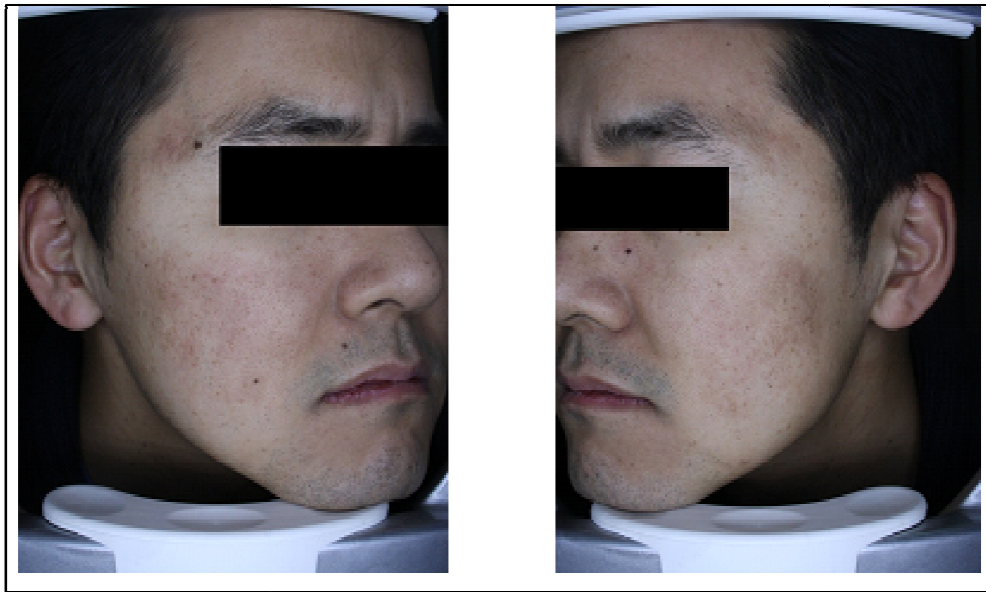


Figure 4. 2 weeks post treatment: Experiment side

2 weeks post treatment: Control side

Folliculitis post treatment was noted in 12 patients (39%). Folliculitis appeared on the control side only in 9 patients (29%), experimental side only in 1 patient (3%), both sides

in 2 patients (6%), and neither side in 20 patients (65%). The difference of folliculitis appearance between the two groups was statistically significant (**Figure 2 and 5**), ($p < 0.05$).

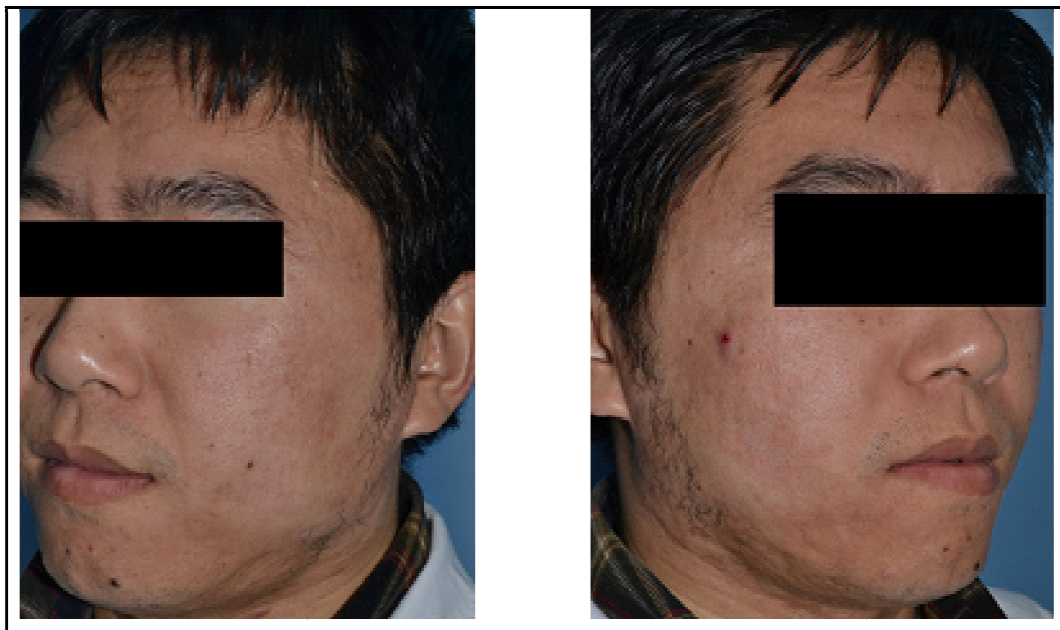


Figure 5. 2 weeks post treatment: Experiment side

2 weeks post treatment: Control side

DISCUSSION

Transdermal drug delivery is the route of administration where active ingredients are delivered through the skin. The direct route in which drugs directly pass through is through

the stratum corneum, but at the same time it is quite thick and difficult to permeate through, posing as the main barrier to transdermal transport. Fractional CO₂ laser creates micropores, allowing better and faster drug absorption. In addition, as the hyperemic blood flow increases after

treatment, so does the concentration gradient between the epidermis and the dermis, which increases permeability, resulting in better absorption, which is further enhanced by saran wrap occlusion.

Recently, studies on the effects of laser treatment and transdermal drugs have been surfacing. Tan et al. [8] observed the efficacy of fractional CO₂ laser with the use of topical ointment "MEBO" on the treatment of hypertrophic scars, results indicated the effects of combinational use was very favorable. Higher efficacy, enhanced wound healing, shorter downtime, and reduced adverse effects were observed. Zhu et al. [9] research on the effects of recombinant human epidermal growth factor derivatives spray after laser treatment showed similar results. Currently, few studies have been completed on the combination use of laser treatment and PRP [10-14].

In recent years, studies have proven the role of growth factors in wound repair [15].

In this study, we took advantage of the micropores produced to increase transdermal drug delivery and chose the timing when permeability of drugs have been increased and topically applied and occluded for 20 minutes autologous concentrated platelet plasma. Results indicated that autologous concentrated platelet plasma (growth factors) combined with fractional ablative CO₂ laser treatment for atrophic acne scars can alleviate skin reactions, enhance wound healing, and reduce adverse effects.

Autologous Concentrated Platelet Plasma

Choukroun et al [16] platelet rich fibrin (PRF) extraction method is very simple, and does not require addition purchases of any special equipment. First, blood is drawn into a glass tube without an anticoagulant, then immediately centrifuged. Three layers will appear: red blood cell layer, PRF clot, and platelet poor plasma (PPP) layer. The PRF clot slowly releases numerous platelets and growth factors, and is only suitable for large open wounds or fillings.

This study used the same principle as Choukroun's PRF preparation to prepare autologous concentrated platelet plasma. Besides advantages of a simplified preparation and lack of biochemical handling, the platelet poor plasma (PPP) was not discarded, (most methods discard the PPP). Although the platelet volume of PPP is lower than PRP, studies have proven the amount of growth factors PDGF- $\alpha\beta$ and TGF- β 1 in PPP is higher than whole blood [17]. In addition, PPP can increase the proliferation of dermal fibroblasts and procollagen type 1 carboxy-terminal peptide (PIP) [18], which is expedites wound repair.

Skin Reactions

Erythema and edema are normal skin reactions after laser therapy. Ong et al. [19] summarization of 13 research papers from 2003 to 2011 on fractional ablative CO₂ laser treatment indicated the average erythema duration time to be 3-14

days, and average edema duration time was 1-3 days [20]. Our study revealed erythema reduction time and total duration was both faster on the experiment side. However, for edema, edema improvement and duration time in this study was very similar between the two groups. This may be contributed by individualized edema reactions.

Pain tolerance differs from person to person, but it normally subsides 1 hour post treatment [20]. In our study, pain scores 12 hours post treatment was less severe on the experiment side.

Wound Repair

Crusting is an important indication of wound repair. Results indicated initial time that crusting appears and initial time that the crust starts to peel was faster on the experimental side, but the time it takes for the crust to peel completely was the same.

Adverse Effects

The incidence rate of postinflammatory hyperpigmentation after fractional CO₂

Treatment is 1-32%, with darker skin color being more prevalent [22]. In our study, out of the 6 (19.4%) patients with PIH, the majority (83.3%) had Fitzpatrick skin phototype IV, which is more prevalent for PIH to appear. PIH grade was higher in the control side, and the difference between the two groups was statistically significant.

When the skin barrier is temporarily breached after treatment, the chances of infection increases. Some patients are prophylactically given oral or topical antibiotics either post or pre laser treatment [19,22], however, topical antibiotics are not advised due to the risk of contact dermatitis [23,24]. The incidence of folliculitis in our study was higher than other reports, this may be because no antibiotics were prescribed, and some patients had a few inflammatory papules or pustules when admitted. However, when compared, the incidence of folliculitis was still lower in the experimental side, indicating that autologous concentrated platelet plasma can reduce post treatment infection, and does not have a risk inflicting contact dermatitis.

From this study, we conclude that we established a simple and economically feasible method to obtain autologous concentrated platelet plasma, which can effectively reduce erythema and pain, enhance wound healing, and reduce adverse effects such as PIH and folliculitis after laser treatment.

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