Evaluation of the Effect of Platelet-Rich Plasma on Recovery After Ablative Fractional Photothermolysis

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IMPORTANCE Despite the advantages and reduced recovery time of ablative fractional photothermolysis, patients still seek adjuvant treatments to reduce healing time and facilitate their return to normal social and work activity. Platelet-rich plasma (PRP) has been used for many applications in various surgical fields for its ability to improve wound healing, hemostasis, and graft survival.

OBJECTIVE To determine whether PRP will be an effective adjunctive treatment to fractional carbon dioxide resurfacing and reduce healing time and duration of adverse effects.

DESIGN, SETTING, AND PARTICIPANTS Prospective blinded study of male and female patients 18 years or older and with Fitzpatrick skin types I to IV performed at Miami Institute for Age Management and Intervention.

INTERVENTION OR EXPOSURE Using a fractional carbon dioxide laser (60 mJ at 150 Hz), a 1-cm² area was treated on each forearm of every patient. Immediately after the laser treatment, patients were randomized to receive PRP in the right or left forearm and saline in the other forearm. Pictures of each forearm were taken immediately after injection of PRP and then on a daily basis until reepithelialization (eschar formation) occurred.

MAIN OUTCOME AND MEASURE Posttreatment erythema, edema, and reepithelialization.

RESULTS Significant improvement in posttreatment erythema was observed in PRP-treated arms across 94 comparisons in 15 patients. Improvement was defined as the erythema rating of the untreated arm minus the erythema rating of the PRP-treated arm. The mean (standard error of the mean) improvement in grade was 0.26 (0.092; t statistic, 2.83; \( P = .003 \)). A mean (standard error of the mean) improvement in edema grade of 0.13 (0.059) was also significant across 94 comparisons (t statistic, 2.20; \( P = .02 \)). Our preliminary results suggest that PRP can objectively reduce erythema and edema following carbon dioxide fractional laser treatment. Most importantly, patients themselves have noticed a reduction in the common posttreatment effects: erythema, edema, pruritus, and discomfort.

CONCLUSION AND RELEVANCE We anticipate that PRP can be an efficacious adjunctive treatment to carbon dioxide laser resurfacing and can aid patients in hastening their return to their normal routine.

LEVEL OF EVIDENCE 1.

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Skin resurfacing and rejuvenation underwent a significant evolution with the introduction of lasers, and ablative carbon dioxide lasers were long considered the gold standard in the resurfacing of photodamaged skin. Unfortunately, the recovery time from treatment with original ablative carbon dioxide lasers was considerable. Patients would spend weeks to months experiencing prolonged erythema, edema, infections, pigment changes, and scarring. Nonablative lasers were developed, but they could not produce the same results as dermal collagen remodeling that the ablative lasers could. In 2004, Manstein et al introduced the concept of fractional photothermolysis (FP) using a nonablative laser. With FP, an infrared laser was used to create microscopic treatment zones. These zones are adjacent to intact tissue and allow for rapid reepithelialization and wound healing. In 2007, Hantash et al applied the concept of FP to the use of the ablative carbon dioxide laser, and they were able to show, in vivo, persistent collagen remodeling for up to 3 months after treatment.

Since the advent of ablative FP, many studies have been published on the decrease in negative posttreatment effects that were commonly seen when using the traditional ablative lasers. Despite this improvement in the adverse effect profile of ablative FP, physicians and patients continue to seek adjunctive treatments that can improve healing time even more. Platelet-rich plasma (PRP) is currently being used in a wide array of clinical disciplines, such as orthopedic and cardiac surgery. Platelet-rich plasma has been found to improve wound healing, hemostasis, and bone graft survival. It is worthwhile to note that the act of PRP preparation does not require US Food and Drug Administration (FDA) approval. Because it is an autologous blood product, administration and preparation of PRP would be similar to giving a patient an autologous blood transfusion. The only component of PRP preparation that has required FDA approval is the centrifuge machine. While a standard laboratory centrifuge can be used, newer cell separator machines and salvage devices that claim to harvest high concentrations of PRP typically require FDA approval. Regardless of the harvesting method, the platelets in PRP become activated and release cytokines and growth factors that promote wound healing.

Patients are consistently concerned about the recovery time after laser skin resurfacing, and they request the use of adjunctive measures to decrease recovery time after treatment. The aim of this study is to evaluate the effect of PRP on healing after treatment with an ablative carbon dioxide laser. We hypothesized that applying PRP to areas treated with ablative fractional carbon dioxide laser will improve healing, but, more important, decrease the duration of obvious adverse effects of erythema and edema. We anticipate that PRP will become a powerful adjunctive treatment to skin resurfacing and aid in allowing patients to quickly return to their pretreatment level of activity.

Methods

This was a prospective blinded study that was in full conformance with the principles of the Declaration of Helsinki, the Belmont Report, the Nuremberg Code, and Good Clinical Practice. The study was given institutional review board approval by Chesapeake IRB. All participants were informed that they could withdraw from the study at any time and all signed an informed consent after review of the risks of the treatment; patients were compensated for their participation. All components of the study were performed at the Miami Institute for Age Management and Intervention.

Our study population included both male and female patients 18 years or older with Fitzpatrick skin types I to IV. We excluded Fitzpatrick skin types V to VI owing to the unacceptable risk of permanent pigmentation changes from laser resurfacing in these populations. Patients were also excluded if they were younger than 18 years or unable to give their own consent, had any dermatologic condition or systemic disease that affected their skin, had undergone any skin resurfacing treatment (laser, topical, radiation) of the test area in the prior 6 months, were taking blood thinners or systemic retinoids, or had any type of coagulopathy. All patients in the study were volunteers, and the study remained open until 15 volunteers were enrolled.

The test sites for this study were both left and right forearms. The coinvestigator (H.K.) designated one forearm as the control arm, and the other forearm to receive the PRP. Every other patient was designated to receive PRP in the right forearm as he or she was enrolled. Only the coinvestigator knew which arm received the PRP and kept a separate record of these data. This effectively blinded the participant and the final assessing physician who would grade each forearm after treatment. Before treatment, a vial of each volunteer’s blood was collected in a BD Vacutainer CPT Preparation tube. The anticoagulant solution in these tubes separates the components of the plasma by weight and increases the concentration of platelets.

Each patient’s blood was then spun down at 3100 rpm for 9 minutes in an 80-2C low-speed centrifuge. After 1 spin cycle, each tube was then gently inverted to resuspend the platelets in the plasma. After resuspension, 1 mL of this PRP was removed and set aside for injection after carbon dioxide laser treatment. While each patient’s blood was undergoing preparation, a thin layer of 20% benzocaine, 6% lidocaine, 4% tetracaine cream was applied to each forearm. Each patient was given 30 minutes of topicalization with the cream prior to carbon dioxide laser treatment. Before laser treatment, all cream was removed with isopropyl alcohol and allowed sufficient time to dry completely.

The coinvestigator then treated an area measuring 1 cm² on each forearm with the Miami Institute’s fractional carbon dioxide laser (Lumenis UltraPulse). We used typical settings that are used for facial resurfacing (60 mJ at 150 Hz, pattern number 3, and spot density of 5). Immediately after laser treatment, the coinvestigator injected the patient with 1 mL of his or her own PRP subcutaneously in one forearm at the apex of the antecubital fossa and 1 mL of preservative-free, injectable saline in the other. Photographs were taken of both forearms on the treatment day (day 0), and every subsequent 2 to 3 days until reepithelialization had occurred and for several days after until the erythema had resolved. The coinvestigator monitored all patient test sites for signs of infection during the course of this study.

At the completion of the study, each patient’s pictures were compiled and organized individually. Another licensed plastic surgeon at the Miami Institute examined photographs of each treatment site and graded them for edema, erythema, and reepi-
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This physician was blinded to the identity, sex, and treatment of each forearm (ie, which forearm received the PRP and which arm received the saline). In addition, this physician was blinded as to the day posttreatment of each photograph. Edema and erythema were graded on a 0 to 4 scale (0, none; 1, trace; 2, mild; 3, moderate; 4, severe). Photographs were also monitored for reepithelialization as being present or absent. At the completion of the study, all participants took a self-administered survey comparing erythema, edema, pruritus, and pain between their right and left forearms. At this time, they were all still blinded as to which arm had received PRP and which arm had received saline after carbon dioxide treatment.

By having each patient serve as his or her own control, we were able to conduct a paired t test on the mean of the differences between the PRP- and saline-treated forearms of each patient.

Results

Results of Photographic Evaluation

Figure 1 and Figure 2 show the general trend for difference in erythema and edema grade, respectively, of saline-treated forearms minus PRP-treated forearms in 4 indi-

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Figure 1. Difference in Erythema Grade of the Saline-Treated Forearm and Platelet-Rich Plasma (PRP)-Treated Forearm in 4 Individual Patients

Each line represents a different patient over the timeline, showing the grade (0-4) of erythema of the saline-treated forearm minus the grade (0-4) of the PRP-treated forearm. In these 4 patients, the saline-treated arms had a higher grade and therefore worse erythema after treatment. This accounts for the positive value when the grade of the saline-treated arm is subtracted from the grade of the PRP-treated arm.

Figure 2. Difference in Edema Grade of the Saline-Treated Forearm and Platelet-Rich Plasma (PRP)-Treated Forearm in 4 Individual Patients

Each line represents a different patient over the timeline, showing the grade (0-4) of edema of the saline-treated forearm minus the grade (0-4) of the PRP-treated forearm. In these 4 patients the saline-treated arms had a higher grade and therefore worse edema after treatment. This accounts for the positive value when the grade of the saline-treated arm is subtracted from the grade of the PRP-treated arm for each patient.

Figure 3. Average of Differences in Edema Rating of the Saline-Treated Forearm vs the Platelet-Rich Plasma (PRP)-Treated Forearm of All 15 Patients

For all 15 patients over 16 days, the mean of differences between the saline-treated and PRP-treated forearms was found to be statistically significant (P = .02) by a paired t test.

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individual patients. A positive value indicates a positive difference and that there was more erythema or edema in saline-treated arms than in PRP-treated arms. We determined the differences between the saline and PRP-treated arms for all 15 patients and performed a paired t test on the mean of all the differences, which yielded 94 observations. We

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<th>Figure 4. Average of Differences in Erythema Rating of the Saline-Treated Forearm and Platelet-Rich Plasma (PRP)-Treated Forearm of All 15 Patients</th>
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<td>Days Posttreatment</td>
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The erythema grade (0-4) of the saline-treated forearms minus the grade (0-4) of PRP-treated forearms. For all 15 patients over a 16-day period, the mean of differences between the saline- and PRP-treated arms was found to be statistically significant (P = .003) by a paired t test.

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<th>Figure 5. Photographic Comparison of Saline-Treated and Platelet-Rich Plasma (PRP)-Treated Forearms of 2 Individual Patients</th>
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<td>A and B. An assessor graded each picture after completion of the project and was blinded as to which arm received PRP and which day was being graded. A, A single patient who had PRP injected into the left forearm and saline in the right forearm. B, A single patient who had PRP injected into the right forearm and saline in the left forearm.</td>
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defined improvement as the grade of the untreated arm minus the grade of the PRP-treated arm. We found that across 94 observations there was significantly ($P = .02$) less edema in the PRP-treated arm, with a mean (standard error of the mean) improvement in grade of 0.13 (0.059; $t$ statistic, 2.20). Across 94 observations, we also found a statistically significant improvement in erythema ($P = .003$) in PRP-treated arms with a mean (standard error of the mean) improvement in grade of 0.26 (0.092; $t$ statistic, 2.83). We also noted an additional trend for the greatest difference in edema between the saline- and PRP-treated arms occurring during the first week (Figure 3). Some patients had the greatest difference in erythema between arms in the first week and some in the second week (Figure 4). We did not note any difference in reepithelialization rates for any of the participants.

Figure 5 depicts the difference between the PRP- and saline-treated forearms. One patient (Figure 5A) had PRP injected into the left forearm, and the other patient had PRP injected into the right forearm (Figure 5B). The differences between the PRP- and saline-treated sites can be visualized in the pictures. The PRP-treated forearms had less surrounding erythema outside of the treatment areas, and the erythema of the treatment site itself was less intense. In addition, erythema and edema dissipated from PRP-treated sites faster than from saline-treated sites overall.

Results of the Patient Survey

The most noted posttreatment effect by the participants was erythema, followed by edema, pain, and pruritus, respectively (Figure 6). Of the 14 patients who noted posttreatment erythema, 71% noticed improvement in posttreatment edema in the PRP-treated forearm. Nine patients noted posttreatment edema, and 67% of these patients had improvement in the PRP-treated forearm. Six patients noticed posttreatment pain, and, again, 67% noticed improvement in the PRP-treated arm. Only 33% of patients noticed posttreatment pruritus, but 80% of these patients had improvement in the PRP-treated arm.

Discussion

Facial rejuvenation has been revolutionized with the advent of ablative FP and, in particular, the fractional carbon dioxide laser. Despite the undisputed improvement that fractional carbon dioxide resurfacing can provide in overall skin tone, pore size, and pigmentation, many patients are concerned about the standard posttreatment effects of erythema, edema, and reepithelialization. The concern is understandable because every patient is seeking optimal rejuvenation with as little recovery time and evidence of treatment as possible. Although FP resurfacing has improved posttreatment adverse effects, patients consistently ask what else can be done. Countless skin care lines have also developed postpeel and postlaser treatments geared toward facilitating healing; however, unbiased comparisons of all these various products is limited and virtually impossible.

Platelet-rich plasma has been documented in numerous clinical studies for its ability to help heal chronic wounds in head and neck cancer, plastic surgery, cardiac surgery, and bone graft survival in orthopedic and oromaxillofacial surgery. Platelets are integral to both hemostasis and wound healing. Once they arrive at the site of a wound, platelet activation occurs, and numerous wound-healing-promoting proteins are released. The wound-healing proteins include platelet-derived growth factor (PDGF), transforming growth factor (TGF-β), platelet factor 4 (PF4), interleukin 1 (IL-1), platelet-derived angiogenic factor (PDAF), vascular endothelial growth factor (VEGF), endothelial growth factor (EGF), insulin growth factor (IGF), and many more. As one of the first responders to tissue injury, the proteins released by activated platelets further drive the wound-healing process by stimulating wound-healing mediators, and this results in cellular proliferation, collagen synthesis, and more.

We hypothesized that PRP would hasten the healing after ablative FP, namely, fractional carbon dioxide laser. We focused on whether PRP would address the most commonly noted postlaser effects of erythema and edema, and if it would also hasten reepithelialization. We found clinically significant improvement in both erythema and edema when the laser-treated areas were injected with PRP; however, we did not find any significant difference reepithelialization. There is limited literature on the application of PRP after fractional carbon dioxide facial resurfacing. Platelet-rich plasma has been used after fractional carbon dioxide resurfacing for acne scars in one report, which found greater improvement in scarring in the presence of PRP. In addition, both posttreatment erythema and edema were also improved with the use of PRP. Our results were similarly encouraging for the potential role of PRP in healing after laser resurfacing.
Conclusions

The greatest weakness of our study is the use of forearms as the test site instead of the face. However, this could also be considered a strength because this allowed us to test 2 completely separate sites on the same person and allowed each patient to act as his or her own control. In the study by Lee et al, they applied PRP to one side of each patient’s face. Growth factor signaling has local as well as distant effects, and as a result, it would be difficult to treat one side of the face in complete isolation. In the future, we would like to see the efficacy of PRP simply placed on the treated area after laser treatment. This should be just as efficacious because carbon dioxide fractional laser has been investigated as a drug delivery tool. We anticipate that a future study with greater enrollment and investigating the same methods used here, or the alternative mentioned herein, would further solidify the potential use of PRP to aid healing after carbon dioxide laser resurfacing.