Efficacy and safety of platelet-rich plasma for treatment of periorbital hyperpigmentation in patients receiving fractional CO_2 laser: a parallel-group blinded randomized controlled clinical trial

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Background: Among different treatments for periorbital hyperpigmentation (POH), both semi-invasive protocols of fractional CO_2 laser and platelet-rich plasma (PRP) are favored among clinicians and rarely cause complications; however, the level of patients' satisfaction seems to differ across these methods.

Methods: This randomized clinical trial was conducted on 100 patients (98 women; 2 men) between 28 to 62 years of age who complained of POH and referred to the Dermatology Clinic of Rasool Akram Medical Complex located in Tehran in 2017. The patients were randomly assigned to two groups receiving fractional CO_2 laser (group C) and adding PRP treatments plus laser therapy (group CP). The outcome of both treatment protocols was followed 3 and 6 months after the last treatment by standard photography.

Results: The time for swelling after treatment in the C and CP groups was 4.58 ± 0.61 days and 2.94 ± 0.68 days, respectively, which was significantly shorter in group CP ($P < 0.001$). The mean time for erythema disappearance was also shorter in group CP (5.20 ± 0.76 days vs. 3.40 ± 0.76 days, $P < 0.001$). Regarding the trend of the change in the ΔE parameter, it fell significantly in both groups within the follow-up period ($P < 0.001$); however, the mean ΔE was significantly higher in the CP group when compared with the control group ($P < 0.001$). There were no significant or resistant side effects in either treatment group.

Conclusion: Although both therapies are effective and safe, the concurrent use of CO_2 laser and PRP can more effectively reduce the severity of POH with a shorter duration of post-treatment swelling and erythema. Hence, this combination is a superior modality for the treatment of POH as compared to laser therapy alone.

Keywords: hyperpigmentation, darkness, platelet rich plasma, ablation, laser, periorbital hyperpigmentation, fractional CO_2 laser, trial, eye dark circle

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INTRODUCTION

Periorbital hyperpigmentation (POH) is a problem that dermatologists deal with more or less and is also addressed under the following dermatologic problems in the literature: darkening in the infraorbital region; dark circles; periocular hyperpigmentation; periorbital melanosis;

infraorbital discoloration; or idiopathic cutaneous hyperchromic changes of the periorbital region [1-4]. Moreover, it can change the quality of life of the involved patients and their feelings in different emotional situations.

Assessing the clinical appearance can guide the physicians to assign the disorder into pigmented (brown color), vascular (blue/pink/purple color), structural (skin color), and mixed types based on the clinical appearance assessed by the physician. The brown color is attributed to pigmented type (P). A blue, pink, or purple tone in the infraorbital region is related to vascular (V) type. The structural type (S) can be distinguished from other types by structural shadows based on lines across the facial anatomic surface [1-4].

Different types of treatment have been introduced for POH. These types vary from topical depigmenting agents, namely hydroquinone, kojic acid, azelaic acid, and topical retinoic acid, to physical therapies, including chemical peels, surgical corrections, and laser therapy [1-3].

In recent times, lasers have been used extensively in cosmetic dermatology.

Applying a number of noninvasive lasers has yielded good results for POH, acting by modifying the pigmentation and vascularity. There are many laser-based therapies intruded for dark circles: Q switched ruby laser (694 nm), Q switched alexandrite laser, and Nd:Yag laser (1064nm) [1,2]. Recently, platelet-rich plasma (PRP) has been welcomed for managing dark circles due to tear trough deformity and wrinkles. PRP involves the use of a single 1.5 mL intradermal injection inside of the tear trough region and wrinkles. Remarkable and satisfactory results have been reported with this method in infraorbital color homogeneity [5-7].

Our study aimed to compare the effects of CO_2 laser and PRP in the treatment of POH.

PARTICIPANTS AND METHODS

This randomized clinical trial (IRCT2015103118210N4) was conducted on 100 patients aged 28 to 62 years who complained from POH and referred to the Dermatology Clinic of Rasool Akram Medical Complex in Tehran from August 2016 to March 2017. All but two patients were female. The exclusion criteria were: any platelet dysfunction, malignant thrombocytopenia, hemodynamic instability, chronic disorder (diabetes, chronic infection, hematological dyscrasia), local inflammatory skin disorders, active herpetic infection in procedure site, history of anti-inflammatory drugs or corticosteroids within the last one month, systemic use of corticosteroids within the last two weeks, recent fever, skeletal or hematological cancers, or serum hemoglobin level lower than 10 g/dl, pregnancy, or lactation. We did not classify the POH based on probable etiologies like structural, pigmented, vascular or mixed, and so we did not compare our results based on this classification. We recorded lifestyle and demographic data of patients like their sleep, stress, familial history, job, television/laptop or mobile use, and daily study time. Since our study was designed as a randomized trial, we expected a normal distribution of these factors in both groups. The patients were randomly assigned into two groups receiving fractional CO_2 laser or fractional CO_2 laser plus PRP treatments. In the PRP group, a 5 ml venous blood sample was extracted and diluted with 1.5 ml of Adenine Dextrose Citric Acid (ADCA) solution. Then, the solution was centrifuged (4000 rpm), and 2 ml of PRP was extracted. Finally, 1 ml of PRP solution was injected in each side of the POH area immediately after CO_2 laser exposure. In each pint, we injected 0.05-0.1 ml of PRP by a distance of 0.5-1 millimeter. We used the SmartXide DOT/ DEKA fractional CO_2 laser apparatus made by Italy, with a power of 10, stack of 2, and a density of 1. Therapy included three sessions in both groups, with a one-month interval between sessions. The outcomes of both treatment protocols were assessed 3 and 6 months after the last treatment session by standard digital photography. The quantitative evaluation of patients was done by the VisioFace® apparatus based on the ΔE, which means evaluating the difference in darkness quantitatively before and after therapy.

In statistical analysis, results for quantitative variables were shown as mean ± standard deviation (SD); for categorical variables, they were expressed with frequency (percentage). Continuous variables were compared using the t-test or Mann-Whitney test whenever the data did not appear to have normal distribution or when the assumption of equal variances was violated across the study groups. Categorical variables were, on the other

hand, compared using the chi-squared test. Before and after comparisons were made using the paired t-test or Wilcoxon test. P values of ≤ 0.05 were considered statistically significant. For the statistical analysis, the statistical software SPSS version 23.0 for windows (*IBM*, Armonk, New York) was used.

RESULTS

Fifty patients were treated with CO_2 laser (group C), while 50 received CO_2 laser plus PRP (group CP). The two groups were similar in terms of mean age, occupational status, duration of disease, family history of POH, sleep cycle irregularities, atopy, mouth breathing, anemia, long exposure to the sun, history of OCP use, thyroid disorders, use of antipsychotic disorders, and history of wearing glasses ($P > 0.05$). The mean Fitzpatrick skin score was 2.98 ± 0.63 in group C and 2.88 ± 0.63 in group CP, showing no difference ($P = 0.432$). The duration of swelling after treatment was 4.58 ± 0.61 days and 2.94 ± 0.68 days, indicating a significantly shorter time in the CP group ($P < 0.001$). The mean time of erythema disappearance was also shorter in the CP group (5.20 ± 0.76 days vs. 3.40 ± 0.76 days, $P < 0.001$). There were no significant or resistant side effects in either treatment group.

The level of satisfaction was similar across the groups (Figure 1). Patient satisfaction was assessed subjectively in 4 categories: 0-25% improvement: unsatisfied; partially satisfied: 25-50% improvement; satisfied: 50-70% improvement; and completely satisfied: 70-100%. The study showed that 76% of patients in the CP group and 70% of patients in the C group were satisfied or completely satisfied with the treatment, respectively ($P > 0.05$).

Based on the data, adding PRP to CO_2 laser reduced periorbital hyperpigmentation (POH) by 25%, and increased the satisfaction of both the physician and patient.

Regarding the trend of the change in the ΔE parameter (Figure 2), significant reductions were seen in both groups within the follow-up period ($P < 0.001$), though the mean ΔE was significantly higher in the CP group relative to the control group ($P < 0.001$).

In Figure 3, we present the before and after therapy pictures of two sample patients, comparing the results of the C and CP groups. Figure 4 indicates a significant positive response in a patient in the CP group. Finally, Figure 5 shows the change in the ΔE parameter over time in a group C patient.

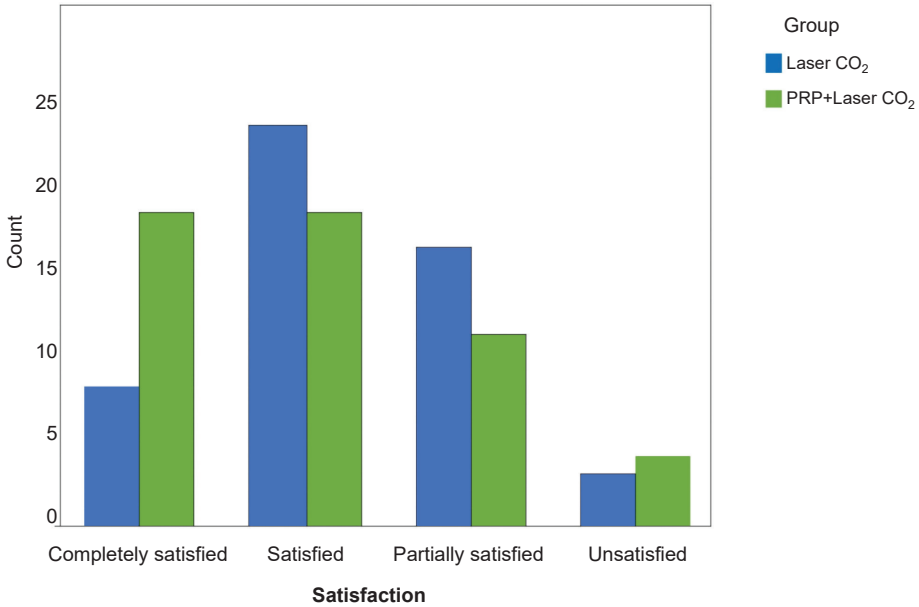


Figure 1. The level of postoperative satisfaction in the C (fractional CO_2 laser) and CP (fractional CO_2 laser + platelet-rich plasma [PRP]) groups.

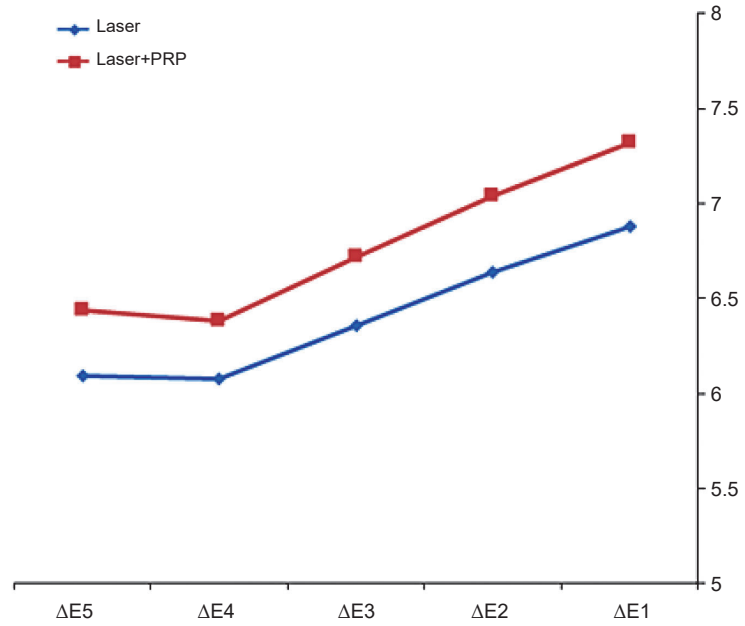
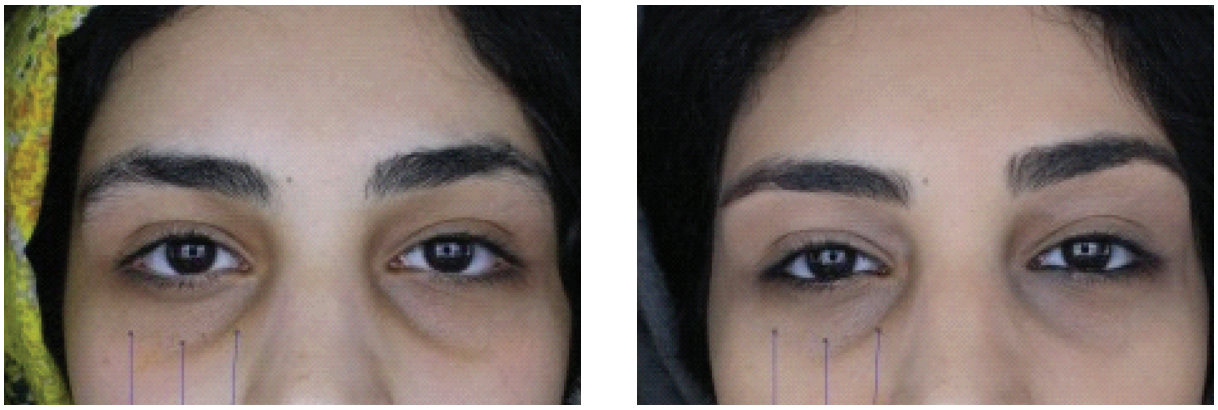


Figure 2. Changes in the ΔE parameter within the follow-up time in the C (fractional CO_2 laser) and CP (fractional CO_2 laser + platelet-rich plasma [PRP]) groups.

Figure 3. Comparison between C and CP groups. Concurrent use of CO_2 laser and PRP could effectively reduce POH and was a superior modality for the treatment of POH as compared to laser therapy alone. A man was treated with fractional CO_2 laser and PRP (a: Before, b: After); A women treated with only fractional CO_2 laser (a: Before, b: After). As it is obvious in both patients, there is a reduction of POH after therapy, but the improvement was greater and more evident with combination therapy.

Before After

Figure 4. A significant response and lightening of periorbital hyperpigmentation using a combination of PRP and fractional CO_2 laser



Before After

Figure 5. Change in the ΔE parameter within the follow-up time of a patient in the CO_2 laser group. As it is visible, the area of darkness and depth of depression of the periorbital region has decreased over time.

DISCUSSION

Among different treatments for POH, both semi-invasive protocols of CO_2 laser and PRP are popular among clinicians and rarely have complications; however, the level of patient satisfaction seems to be different. PRP consists of different growth factors confirmed to be actively secreted. In PRP, adult mesenchymal stem cells, fibroblasts, osteoblasts, endothelial cells, and epidermal cells are the sites where the receptors for growth factors can be found. Fibroblasts are the most common cell type in the dermis, producing collagen and other extracellular components. Fibroblasts are strongly reactive to fibroblast growth factor-beta, platelet-derived growth factor, and epidermal growth factor. PRP induces cell migration and production of fibroblast cells, giving it unique repair and rejuvenation characteristics [7]. Hence, we added PRP to one arm of our study, hypothesizing a better effect with this combination. The positive effect of laser (especially fractional CO_2 laser) on POH has been documented in many studies [8].

Our study compared the outcome of two procedures regarding periorbital swelling and erythema and hyperpigmentation assessed by the change in ΔE parameter. We showed that concomitantly use of CO_2 laser and PRP could lead to more reduction in hyperpigmentation (more ΔE) than CO_2 laser use alone. PRP has a major role in revascularization and collagen and extracellular matrix (hyaluronic acid) synthesis, leading to an increase in the volume and tightness of the skin and giving it a glowing view [9]. In a study in Turkey, the benefits of PRP in removing POH were documented in about 71% of treated patients [10]. Intradermal injection of PRP was also successful in rejuvenating the neck and face and

improving scars [11]. Kang *et al.* [12] also showed that PRP injection could remove POH in 75% of cases. Shin *et al.* [13] also indicated that the use of non-ablative laser fraction plus PRP could increase skin elasticity, improve erythema score, and increase collagen density in 65% of cases. In another survey, using PRP and CO_2 laser reduced wrinkles around the mouth and the eyes in 85% and POH in 60% of cases [14]. In our study, the concurrent use of CO_2 laser and PRP could more effectively reduce the severity of POH, was more tolerable, and was associated with a higher satisfaction rate of patients (although statistically insignificant), making it a superior modality for treatment of POH compared with laser therapy alone. Patients in the combination group experienced higher rates of complete satisfaction. Logically, higher satisfaction with treatment in the PRP+CO_2 laser group was mainly related to the shorter treatment downtime.

In cosmetic dermatology, melasma, acanthosis nigricans, and periorbital hyperpigmentation are common complaints, so researchers have focused on probable associations and promising therapies [8,15-20]. The authors of this study previously evaluated the treatment of dark eye circles with two well-known promising rejuvenating options that work for many cosmetic concerns [19,20], and designed this trial to find a better approach to periorbital hyperpigmentation.

Limitations

For evaluation of satisfaction, we defined a subjective outcome measure and did not use standard questionnaires, which should be done in future studies. We did not classify the POH based on probable etiologies like structural, pigmented, vascular or mixed, so we did not compare our results based on this classification.

CONCLUSION

The concurrent use of fractional CO_2 laser and PRP can more effectively reduce the severity of POH in addition to its shorter downtime (fewer days of swelling and erythema). Hence, combination therapy with fractional CO_2 laser and PRP is a superior modality to treat POH as compared to fractional CO_2 laser therapy alone. The combination method is associated with higher satisfaction of patients with therapy.

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Contributions

All the authors contributed to preparing the final version of this manuscript.

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