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Injectable platelet-rich fibrin for facial rejuvenation: A prospective, single-center study

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Abstract

Background: Autologous platelet-derived preparations have been used in many surgical fields to improve healing outcomes, with benefits reported in several aesthetic indications.

Aims: This single-center, prospective, uncontrolled study evaluated the efficacy of injectable platelet-rich fibrin (i-PRF) for facial skin rejuvenation using an objective skin analysis system and validated patient-reported outcome measures.

Patients/Methods: PRF® PROCESS system technology was used to prepare i-PRP. Eleven healthy female individuals were included in the study and over 3-months received monthly intradermal injections of i-PRF in 3 facial regions: malar areas (1 mL each side), nasolabial fold (0.5 mL each side), and upper lip skin above the vermilion border (1 mL). The efficacy of the procedures was assessed by objective skin analysis (VISIA®) and a subjective patient-reported outcome (FACE-Q) assessment at baseline and after 3 months.

Results: A significant improvement in skin surface spots ($P = .01$) and pores ($P = .03$) was seen at 3-months follow-up. Other variables, such as skin texture, wrinkles, ultraviolet spots, and porphyrins, showed a numerical improvement. FACE-Q scales that measure satisfaction with appearance all showed a significant improvement from baseline, including satisfaction with skin ($P = .002$), satisfaction with facial appearance ($P = .025$), satisfaction with cheeks ($P = .001$), satisfaction with lower face and jawline ($P = .002$), and satisfaction with lips ($P = .04$). No major adverse effects were reported.

Conclusions: A series of three i-PRF injections resulted in significant rejuvenation of the face skin at 3-month follow-up, as shown by improved skin analysis parameters and patient self-assessment scores.

KEYWORDS

FACE-Q, facial rejuvenation, platelets, PRF, VISIA

Level of Evidence: Level IV, therapeutic study.

1 | INTRODUCTION

Aesthetic medicine practice has recently witnessed a proliferation in the number of injectable platelet concentrate products containing supra-physiological quantities of platelets and autologous growth factors to stimulate tissue repair and skin rejuvenation.[1-4] Growth factors contained within these plasma concentrates have emerged as a promising therapeutic modality by regulating important processes in skin rejuvenation,[5] including angiogenesis, cell migration, cell proliferation, and collagen deposition.[6]

Platelet-rich plasma (PRP) and plasma-rich growth factors (PRGF) were the first plasma concentrates to be developed in 1998 and 1999, respectively.[1,7] Both systems require addition of bovine thrombin or calcium ions during initial blood collection to activate platelet growth factor release[2] followed by nonautologous anticoagulants to generate fluid concentrates after centrifugation. A two-step centrifugation is required to produce PRP, which is predominantly composed of platelets and growth factors with a limited number of leukocytes. PRP is widely used across a range of medical and oral specialties, as a tool for tissue regeneration.[8-11]

For facial skin aging, PRP use is associated with modest improvement in facial skin appearance, skin texture, and lines.[12] However, the clinical evidence for PRP use in this indication is limited by heterogeneity in the preparation and administration techniques used, and lack of standardization in outcome measures.[12] Despite the widespread use of PRP, concerns have been raised about the use of thrombin and anticoagulants that can impair wound healing by inhibiting the coagulation process.[13]

To overcome some of the limitations of PRP, platelet-rich fibrin (PRF), a second-generation platelet concentrate was developed in 2001.[14] It is obtained using a one-step centrifugation process without the use of anticoagulants and thereby totally autologous. The resulting product contains cell types (platelets, leukocytes, red cells), an extracellular fibrin matrix, and an array of bioactive molecules (predominately growth factors).[15] Depending on the blood collection tube and centrifugation protocol used, solid gel and liquid forms of PRF can be developed. Solid PRF, produced using glass tubes has been successfully used in oral and maxillofacial surgery, with beneficial effects on bone and soft tissue regeneration, infection control, and patient satisfaction.[13,16] In plastic surgery, solid PRF has demonstrable benefit in soft and bony tissue healing as well as fat graft survival rate.[17] In 2014, an injectable fluid form of PRF (termed i-PRF) was developed by modifying the relative centrifugal force (RCF).[18] By lowering the centrifugation speed and time, and by using plastic tubes (to reduce clotting times), the fibrin coagulation could be slowed at early time points thereby generating a liquid PRF.[18,19] The resulting product contains fibrinogen and thrombin that remains fluid for about 20 minutes after centrifugation prior to fibrin formation, thereby making it a suitable injectable material for facial rejuvenation.[20,21] The low speed of centrifugation, just enough to separate platelets from red blood cells, improves the characteristics of the resulting PRF with higher numbers of leukocytes and platelets, and increased growth factor concentration within the resulting fibrin matrix.[22,23] Platelets and cytokines become trapped within the i-PRF fibrin matrix after injection leading to a slow and gradual release of growth factors over time.[19] Use of this injectable form of PRF has been reported for the treatment of various oral and maxillofacial procedures[24,25] and alopecia.[26] Limited data have been reported for its use in aesthetic skin rejuvenation.[27,28]

Here, we report the results of a study that prospectively evaluated the efficacy and safety of i-PRF for use in facial rejuvenation using an objective skin analysis system and a validated patient-reported outcome measure.

2 | MATERIAL AND METHODS

2.1 | Study design and participants

This was a single-center, prospective, uncontrolled, case series of consecutive adults (February to May 2018) seeking autologous platelet-derived growth factors injections to the face. The study was performed following local ethics committee approval (Queen Mary University of London), and written informed consent was obtained from all participants.

Eligible study participants were healthy females aged ≥18 years with no previous facial surgical or nonsurgical aesthetic intervention within 12 months of their first consultation; agreement to avoid facial aesthetic surgical, laser, or cosmeceutical interventions during the treatment/study period; no active dermatological disease; no smoking; and no contra-indication for aesthetic intervention.

The study took place over a 13-week period during which participants attended the aesthetic clinic on five different occasions

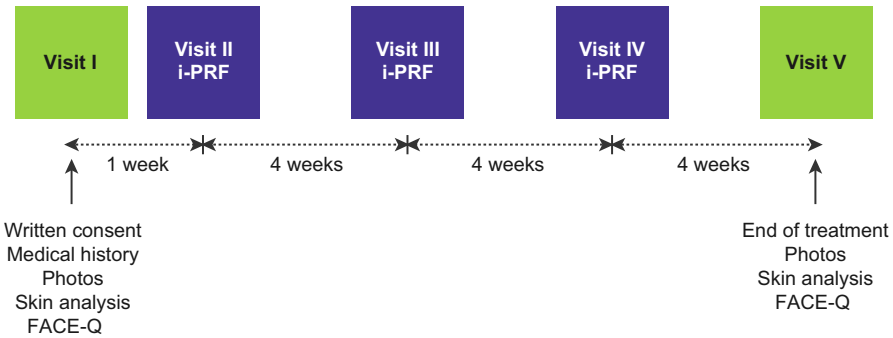

FIGURE 1 Study design

(Figure 1). During visit I (baseline), a full medical history, clinical examination, and detailed information of the study and protocol were provided. Following informed consent, the participant underwent digital skin analysis (VISIA®, Canfield Imaging Systems),[29] standardized 2D clinical photographs, and completed a validated patient-reported outcome measure (FACE-Q).[30] This was followed by 3 treatment periods (visits II through IV), each separated by 4 weeks, during which each participant received i-PRF treatment in three regions of the face. In the final visit V, occurring 4 weeks after the last treatment, the VISIA® digital skin analysis and FACE-Q questionnaires were repeated.

2.2 | i-PRF preparation

At the beginning of each treatment session, 40 mL of peripheral venous blood was collected in sterile 10 mL plastic PRF tubes (Jiangsu Kangjian Medical Apparatus Co., Ltd) (Figure 2A/B) without anticoagulant and centrifuged immediately (Duo Quattro Centrifuge, Process for PRF, Nice, France) at room temperature using a low relative centrifugal force (700 rpm for 3 minutes, 60 g RCF) (Figure 2C), as described previously.[22] This centrifuge has a fixed angle with a radius of 110 mm. The upper 1 mL of the preparation layer (Figure 2D) was then removed using an 18 g 1.5-inch BD™ blunt fill needle (Becton Dickinson, Fraga, Spain) into a 1 mL syringe BD Luer-Lok™ Tip Becton Dickinson

2.3 | i-PRF treatment

Topical anesthetic cream (EMLA 5%, AstraZeneca, Sodertalje, Sweden) was applied for 20 minutes prior to each treatment session. Bilateral intradermal injections into the malar area (1 mL each), nasolabial folds (0.5 mL each), and upper lip skin above the vermilion border (1 mL) were performed using a TSK STERiJECT® 32 g × 4 mm needle (TSK Laboratories, The Hague, The Netherlands) (Figure 3). Individual 0.1-mL injections spaced 5 mm apart were administered to cover the three regions by the same investigator (HH). In total, approximately 4 mL of i-PRF in four 1-mL syringes was administered. Standard postprocedure instructions were given to each participant, including advice about swelling, bruising, pain, and avoidance of sun exposure.

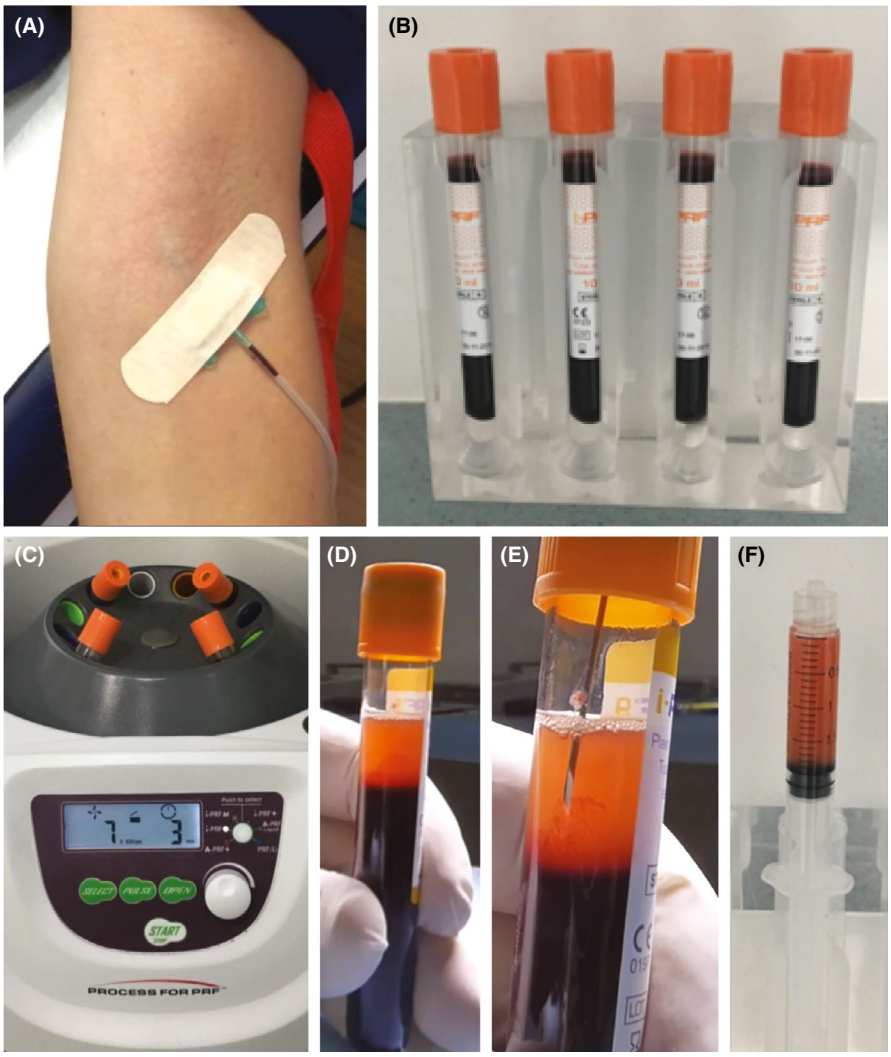

FIGURE 2 Preparation and administration of injectable platelet-rich fibrin (i-PRF) A, venepuncture B, blood samples prior to centrifuge C, centrifuge for 3 min at 700 rpm D, layering of tube E, extraction of top layer using 18 G needle F, i-PRF in 1-mL syringe ready to be injected

2.4 | Skin analysis assessment

VISIA® standard incandescent, cross-polarized, and ultraviolet light skin analysis settings were used to determine the skin conditions at baseline and following treatment by measuring the variables of wrinkles, skin surface spots, texture, pores, ultraviolet spots, porphyrins, red areas, and brown spots (Table 1).[30] To standardize the procedure, all assessments were performed with a clean skin free of makeup. Percentage scores for each parameter were reported, representing the patient's percentile ranking relative to people of the same age, gender, and skin type. Higher percentiles (eg, greater than 50%) indicate the patient's skin is better than the average of her peers. Lower percentiles (eg, less than 50%) indicate the patient's skin is worse than the average of her peers.

2.5 | Subjective assessment

The FACE-Q patient-reported outcome measure was used to provide a subjective evaluation of the treatment. Six FACE-Q scales were used, including two scales that measure satisfaction with their appearance (satisfaction with skin and satisfaction with facial appearance), three that measures satisfaction with area-specific regions of the face (cheeks, lower face and jawline, lips), and a single scale measuring adverse effects of the skin.[31,32] The questionnaires were administered by an independent investigator who was not otherwise involved in the study. Replies for each scale were evaluated using a four-point scale with raw scores added to provide a total score. The total score was then converted to a Rasch transformed score from 0 to 100.[31,33] Higher scores for scales measuring satisfaction with appearance reflect a better outcome, with reduced scores for adverse effects of the skin associated with a better result.

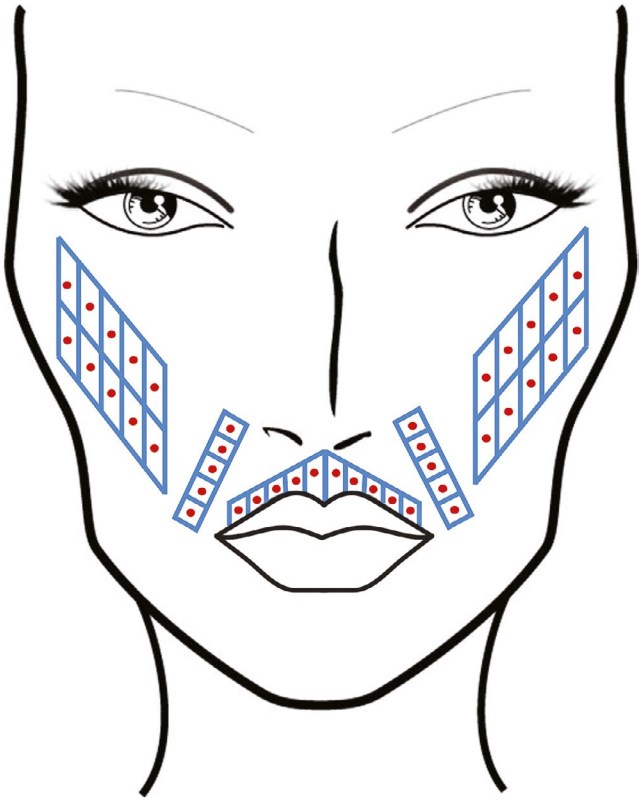

FIGURE 3 i-PRF injection points in the three facial areas. Each point represents a 0.1 mL intradermal injection of i-PRF, 20 points on each side of the face

2.6 | Statistical analysis

Statistical analysis was performed using SPSS® version 19.0.0.1 (IBM, Armonk, NY). Descriptive statistics for quantitative continuous variables with the digital skin analyzer (VISIA®) and subjective assessment (FACE-Q) were summarized as mean ± standard deviation (SD). Student's *t* test (one-sample, paired) was used to compare continuous variables within the same participant before and one month after the three sessions of i-PRF treatment. *P*-values <.05 were considered statistically significant.

3 | RESULTS

Eleven healthy female individuals, mean age 42.2 ± 8.6 years (range 33-60 years), were included and completed the study. Fitzpatrick skin types ranged from I to IV, with types III and IV being the most common (40% each). All the treatment procedures were completed without any complications. Mild bruising attributed to the injection technique was encountered after several treatment cycles, but no serious side effects were reported.

3.1 | Objective VISIA® image analysis

There was a significant improvement in percentile scores for skin surface spots ($P = .01$) and pores ($P = .03$) after 3 months compared with conditions at baseline (Figure 4). There was also a numerical improvement in the percentile scores for skin texture ($P = .17$), UV spots ($P = .50$), porphyrins ($P = .37$), and wrinkles ($P = .27$) compared with the measurements before the first i-PRF injection. Numerically lower percentile scores for brown spots ($P = .46$) and red areas ($P = .59$) were noted at follow-up compared with baseline. Figure 5 shows an example of the photographs generated by the VISIA® system using standard (for spots, wrinkles, texture, and pores), ultraviolet (for UV spots, porphyrin), and cross-polarized (for brown spots, red areas) lighting.

3.2 | Subjective assessment

All subjects completed the FACE-Q self-assessment outcome scores. At 3-month follow-up, all five FACE-Q scales that measure

satisfaction with appearance showed a significant improvement from baseline (Figure 6), including satisfaction with skin ($P = .002$), satisfaction with facial appearance ($P = .025$), satisfaction with cheeks ($P = .001$), satisfaction with lower face and jawline ($P = .002$), and satisfaction with lips ($P = .04$). Numerical improvement was also observed for adverse effects related to skin ($P = .14$).

4 | DISCUSSION

This prospective study evaluated facial aesthetic outcomes following intradermal injection of PRF using a well-described protocol. The efficacy of the procedures was assessed by objective skin analysis (VISIA®) and a subjective patient-reported outcome (FACE-Q) assessment at baseline and after 3 months. Significant improvement in several skin characteristics was mirrored by significant improvement in patient satisfaction, thereby suggesting a benefit for the use of i-PRF for facial skin rejuvenation.

TABLE 1 Skin variables measured by the VISIA® skin analyzer

Variable	Definition
Pores	The circular surface openings of sweat gland ducts
Porphyrins	The bacterial excretions that can become lodged in pores and lead to acne
Texture	Measures the skin color and smoothness
Red Areas	Inflammation or spider veins
Brown Spots	Lesions on the skin, that is, hyperpigmentation, freckles, and melasma
Ultraviolet spots	Occur when melanin coagulates below the skin surface due to sun damage

PRF is an evolution of platelet-rich aggregates, intended to utilize the positive effect of platelet-derived growth factors on tissue healing and regeneration.[34-36] It differs from other platelet-rich concentrates such as PRP and PRGF in two key aspects. First, PRF is a total autologous, unaltered platelet-based aggregate that requires no additives to anti-coagulate the blood or activate the platelets.[14] Second, PRF uses a relatively low centrifugation speed to ensure successful capture of both platelets and circulating blood regenerative cells, leading to an increased concentration and prolonged effect of growth factors.[37] In addition, PRF has been shown to have higher values of platelets, fibrin, growth factors, and leukocytes compared with PRP and PRGF leading to a more enhanced growth factor-mediated functional outcome.[38] Leukocytes play an important role, via a cluster of mesenchymal stem cells, with important regenerative functions, including stimulation of fibroblast propagation, improved anti-inflammatory effects, angiogenesis, and protein deposition (eg, procollagen) for extracellular matrix remodeling.[39] The low centrifugation speed of PRF results in a higher number of cells, including leukocytes, within the supernatant product before formation of a fibrin clot.[40]

In this study, we documented the clinical outcomes of i-PRF injections by means of objective measurements with a noninvasive skin analysis device (VISIA®). A significant improvement in the percentile scores was observed in skin surface spots and pores with a numerical improvement for most of the other parameters. Improvement in these parameters assessed using the VISIA® system has also been observed in other studies evaluating the efficacy of PRP injections for facial skin rejuvenation.[41,42]

In this study, the FACE-Q patient-reported outcome tool was completed by patients at baseline and at the end of treatment. The main purpose was to consider the patient's viewpoint on the effects of the treatment being provided and their satisfaction with various related characteristics. Six scales were used, 5 measuring satisfaction with appearance and one related to adverse

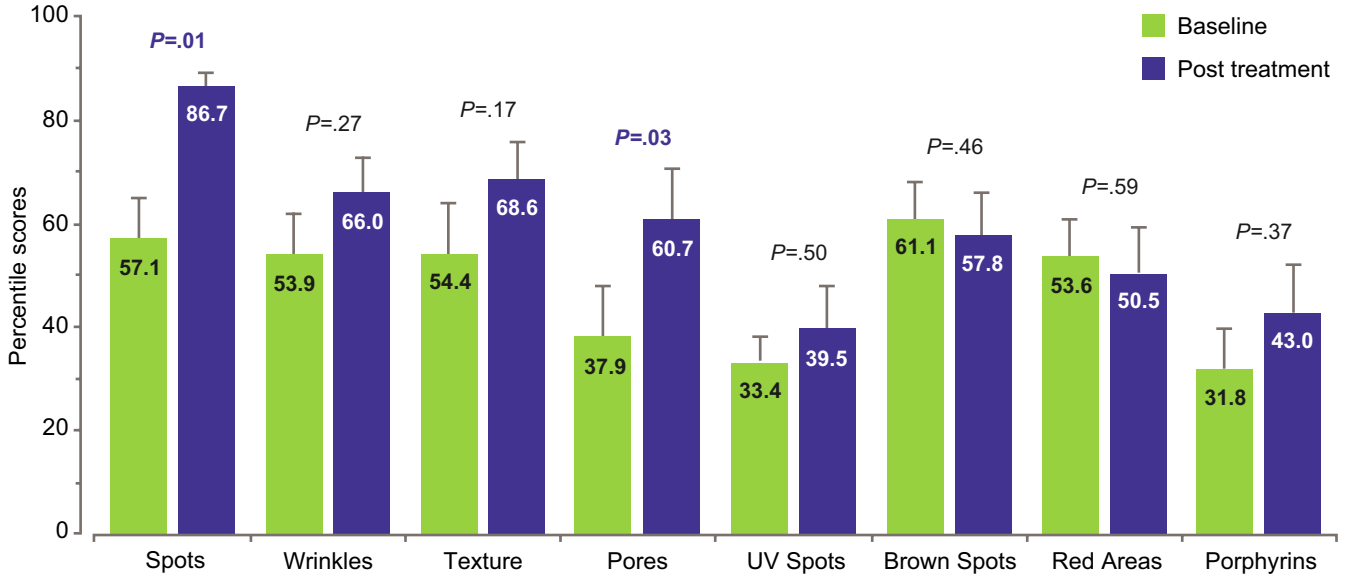

FIGURE 4 Mean (± SE) percentile scores for different variables measured by VISIA® skin analysis at baseline and at 3-month follow-up following three i-PRF treatment sessions

FIGURE 5 VISIA® complexion analysis of a 48-year-old Middle-Eastern woman at baseline (A) and at 3-month follow-up following three i-PRF treatment sessions (B). Percentage scores for each of the eight measured parameters are shown, representing the patient's percentile relative to age, gender, and skin matched controls. Higher percentiles (eg, greater than 50%) indicate the patient's skin is better than the average of her peers. Lower percentiles (eg, less than 50%) indicate the patient's skin is worse than the average of her peers

effects. Overall satisfaction with facial and skin appearance was improved (75.4 ± 19.4 and 79.1 ± 17.6 at follow-up, respectively) along with an improvement for each of the specific facial areas evaluated. Looking at specific areas, more prominent satisfaction was observed for the cheeks (mean satisfaction score 86 of 100) and the lower face and jawline (84 of 100). As expected, participants were least satisfied with their lips (66 of 100) at follow-up. In view of the low baseline score for skin adverse effects (29 of 100), the lack of a statistically significant improvement is not unexpected. To the best of our knowledge, only two studies have used the FACE-Q to evaluate patient-reported outcomes following use of PRP or PRF monotherapy for facial rejuvenation.[43,44] In one study, Lee and colleagues showed improvement in participant satisfaction with overall facial appearance and cheeks following a single injection of PRF[43] while in the other study Nacopoulos and colleagues that reported an improvement in the satisfaction with skin questionnaire following several sessions of injectable PRF treatment.[44]

To our knowledge, the clinical use of injectable PRF for facial aesthetics has only been previously reported in a single study. Nacopoulos and Vesala recently reported on the use of a combination of liquid PRF matrices for lower facial rejuvenation.[28] Using a standardized protocol over 4 treatment sessions (each separated by 2- to 3-week intervals), 10.5-13.5 mL of the PRF product was injected (intradermal and subcutaneous) per session in 34 patients. The PRF used in this study was prepared by combining i-PRF centrifuged at low speed (700 rpm for 3 minutes, 60 g RCF [3-4.5 mL]) with a PRF matrix (termed advanced-PRF-liquid) designed to provide volumization (1300 rpm for 5 minutes, 208 g RCF [7.5-9 mL]). These two products were mixed in the same syringe prior to injection. Clinical outcomes were assessed by 23 independent blinded reviewers who compared before and after treatment photographs. In the initial assessment just prior to the second session, only 47% correctly identified the correct order of the photographs among 23 evaluable participants. By the second photographic assessment after the completion of treatment, 60%

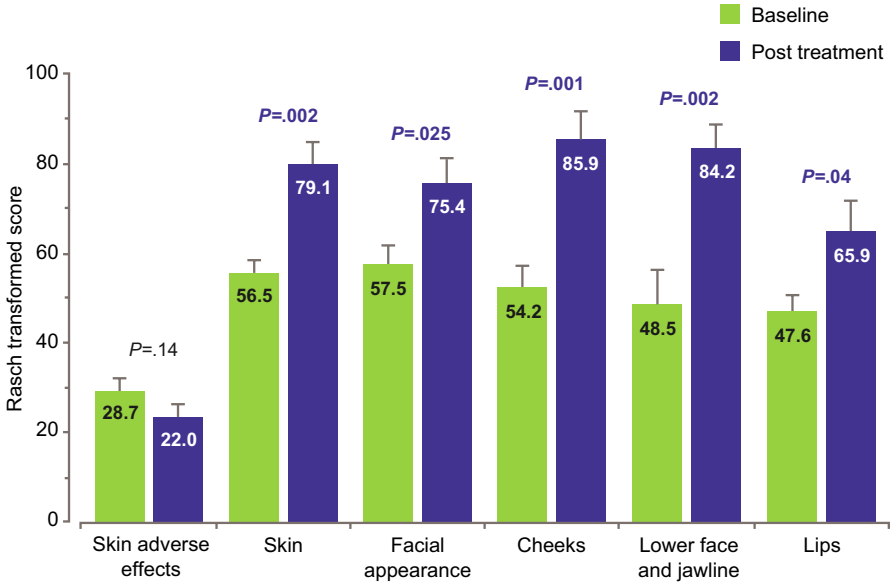

FIGURE 6 Mean (± SE) Rasch transformed scores for different FACE-Q scales at baseline and at 3-month follow-up following three i-PRF treatment sessions

TABLE 2 Characteristics of i-PRF used in this study adapted from the proposed FIT PAWW classification[47]

Acronym	Description	Study results
F	Force of centrifugation	60.3
I	Iteration or sequence of centrifugation	Centrifugation only
T	Time of centrifugation	3 min
P	Platelet concentration	531 x 10^9/L[a]
A	Anticoagulant use	Nil
A	Activator (type and amount)	Nil
W	White blood cell count[a]	7.53 x 10^9/L[a]
F	Fibrin presence	Yes

[a]Based on data reported by[51] using a similar protocol for preparation of i-PRF.

of the reviewers correctly identified the correct order ($P < .001$ vs the initial assessment). This subjective method of assessment may have introduced a bias with respect to the identification of the photograph order. Further, the combination of two PRF preparations in the study, one of which had a marked volumization effect, precludes any direct comparison with the results of our study where only small volumes of a single i-PRF product (eg, 0.5 mL versus 3 mL each side in the nasolabial folds) were administered to three regions in the mid and lower face.

Various attempts have been made to standardize the reporting of PRP and PRF preparations to enable comparisons across trials for different treatments.[45-49] For PRP, Frautschi and colleagues[47] noted the lack of consistent reporting of composition, dosing, activation, and the use of subjective rather than objective outcome measures. They suggest the use of a set of descriptors, described by the FIT PAWW acronym to facilitate standardized reporting of PRP methodologies. To facilitate future comparisons of injectable platelet concentrates, this index could be modified to include fibrin (F) as a new component. Table 2 summarizes these features in respect to the preparation of PRF in our study. For PRF use, Miron and colleagues (2019)[48] have recommended necessary parameters for reporting RCF values for studies evaluating PRF products. Unfortunately, none of these parameters incorporate all of the elements that might help to differentiate the various available injectable PRP and PRF preparations. Future standardized reporting of the concentrations of administered growth factors, platelets, and leukocytes might help to provide useful information to enable comparisons between studies. Unfortunately, the design of our study prevented this information from being reported.

The injectable form of PRF used in the study was prepared using a short and slow centrifugation speed (3 minutes at 700 rpm) that resulted in a platelet concentrate that contained a high concentration of growth factors compared with earlier more solid formulations of PRF that were prepared using higher centrifugation speeds.[22] In recent years, alternative protocols to further improve the platelet and leukocyte yields of injectable PRF have been evaluated.[50] These include increasing the time of centrifugation time (eg, from 3 to 4 to 8 minutes to further accumulate platelets in the upper i-PRF layer),[22] and using a horizontal centrifuge rather than the conventional fixed-angle centrifugation to increase platelet and leukocyte yields.[51] Our study used a centrifugation speed and time recommended for use in females.[28] For male subjects, an increased centrifugation time of 4 minutes is recommended as they tend to have a higher red cell counts compared with females. Additional refinements to the i-PRF preparation used in our study have also been made to increase in tube size (from 10 to 13 mL) and increase the centrifugation time (from 3 to 5 minutes at 700 rpm), both of which result in an increased volume of i-PRF (from 1 to ~2 mL) along with an increase in the number of platelets (up to 645,000 for each μL) and mesenchymal stem cells (up to 63 000 for each μL).[52] This new i-PRF preparation, called i-PRF+, is more suitable for use in aesthetic procedures. The constantly evolving protocols used to prepare these injectable PRF products highlight the need for further research to

demonstrate the comparative effectiveness of each preparation in aesthetic procedures.

Limitations exist with this study. First, the small number of participants meant there was limited statistical power for the assessment of the clinical outcomes. Aesthetic medicine research is challenging as most participants are self-paying individuals who do not want to be included in such evaluations. Studies reporting clinical outcomes with platelet aggregates for aesthetic treatment typically include 10 participants or less.[2,53-55] Second, the lack of a control group could have influenced the subjective outcomes. This study was approved as prospective case series (audit of practice) to evaluate objective and subjective aesthetic outcomes, thereby preventing the use of a control group or further evaluation of the different blood parameters comprising the i-PRF preparation.[47] Additional limitations include the relatively short-term follow-up period and the limited number of treated areas (malar, nasolabial folds, and upper lip). A larger study would have also allowed for evaluation of the potential cost-effectiveness of i-PRF treatment compared with other skin rejuvenation modalities.

5 | CONCLUSION

In summary, this study demonstrates that intradermal injection of i-PRF is a safe intervention that is associated with favorable objective facial skin aesthetic outcome and improved patient satisfaction. Further multicenter, controlled, and randomized studies with larger sample sizes are required to fully investigate the short- and long-term effects of i-PRF in relation to facial rejuvenation and aesthetic regeneration. Objective outcome measures and validated tools for patient-reported outcomes should be used to evaluate the results.

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CONFLICT OF INTEREST

The authors declare that they have no conflict of interest in this study.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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