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Autologous Platelet-Rich-Fibrin in Esthetic Medicine: Mini Review on the Current Development Stage

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ABSTRACT

The present mini-review on the general and specific aspects of the platelet-rich fibrin (PRF) application technique adopted for dermatological treatments reports differences between platelet-rich plasma (PRP) and PRF, their specific applications in dermatology and preparation methods, mainly with respect to PRF. The protocol for patients undergoing treatment and the ethical aspects that must be addressed by treatment specialists, such as informed consent, are also highlighted. Clinical trials have proven i-PRF (injectable platelet-rich fibrin) to be more effective than PRP in skin regeneration. The i-PRF method accounts for a more sustained and long-lasting release of growth factors (GFs). Furthermore, it proved more effective in most studies in comparison with PRP. Therefore, it is now acknowledged for its several medical and dermatological applications. Finally, PRP and PRF use seems promising given their favorable, safe, and well-tolerated results in improving facial aging signs.

Keywords: *Platelet-rich fibrin; Platelet-rich plasma; Esthetic medicine; Facial rejuvenation; Skin regeneration; Dermatology.*

Introduction

The concept of using collagen bio-stimulation focused on skin quality emerged in 2019. PLLA (poly-L-lactic acid), CaHA (calcium hydroxyapatite), and PCL (polycaprolactone) use was a great evolution, mainly when it comes to their application for facial renovation or rejuvenation purposes. The properties of all these bioproducts, such as PLLA, pointed out their efficiency in continuous dermal reconstruction. CaHA, for instance, provides fast volumization and further bio-stimulation. PCL, in its turn, expresses long-lasting clinical outcomes. Overall, biostimulators have shown benefits and secure outlines, as well as high individual fulfillment rates. However, future investigations must focus on multicenter and long-term clinical assessments to reinforce the current evidence available [13]. However, nonsurgical attempts and the application of PRP made of autologous plasma were approved for facial skin rejuvenation and for other uses [5,48,64]. PRP importance lies in its wide range of proteins/growth factors, including VEGF (vascular endothelial growth factor), PDGF (platelet-derived growth factor), and TGFβ (transforming growth factor beta). These factors account for skin rejuvenation based on angiogenesis enhancement, stem cell stimulation, tissue structure change, cell proliferation/regeneration, and hyaluronic acid generation [48]. Many studies describe the use of anticoagulants and the fast delivery of growth factors as likely PRP drawbacks [12,41,58]. Assumingly, these concerns triggered the need for improving the preparation of second-generation platelets based on blood extraction without anticoagulant and fast direct centrifugation [42]. Platelets and leukocytes in second-generation platelet-rich fibrin (PRF) are captured from the fibrin clot, and growth factors are gradually released over a controlled period-of-time [32]. However, this PRF is not necessarily used to activate growth factors. On the other hand, a low platelet yield count could be assessed as a likely PRF drawback. Another concept to be observed is the injectable PRF re-

sulting from slow-speed centrifugation [8]. Some studies address PRF application for facial skin rejuvenation or for other associated recommendations [4,35,58].

The last few years witnessed PRP approval for use in the regenerative field, mainly in esthetic medicine and in skin aging therapy [40]. Besides, this research area also acts efficiently on cancer [37,38], dental treatment [16], trigeminal neuralgia [17], and cardiovascular disease [18]. PRP is obtained from the patient's autologous blood, and it has GFs (platelet growth factors) capable of achieving tissue repair and collagen production [19,28,31,34]. Nevertheless, the latest research shows that another PRF preparation may present significant regenerative properties due to its three-dimensional fibrin matrix, which allows long-lasting GF release and, consequently, leads to more efficient tissue regeneration. PRP is produced through fast centrifugation aimed at separating platelets without clots. PRF, in its turn, is produced by slow centrifugation without anticoagulants to generate fibrin lattice [7,20,50]. The lattice entraps GF and leads to its gradual and controlled release. This process is perfect for permanent regenerative procedures. Hassan et al. [27] made quite good PRF featuring. They have proven greater skin texture improvement and individual satisfaction with PRF in comparison with PRP. On the other hand, besides inducing tissue healing due to its structure, PRF also enables the formation of new blood vessels and controls inflammation processes, which are important components of total skin recuperation. Moreover, different research has suggested further PRF progress due to CGF (concentrated growth factors), which normalizes GF concentration and assumingly represents one of the most favorable alternatives in the regenerative field. Although PRP is a feasible option for skin regeneration, PRF accounts for new updates given its fibrin matrix and controlled GF release. Accordingly, PRF or CGF can be a selected choice for long-term therapies that require stronger and more substantial production [10,25,51,63].

PRP needs bovine thrombin or calcium chloride, and this is the most important difference between PRF and it. However, the PRF thrombin amounts acting in autologous fibrinogen are totally physiological and do not demand the insertion of external chemical agents [43]. Thus, PRF stands out from PRP for its easy preparation, simple administration, and low cost (close to zero). Furthermore, it significantly reduces blood biochemical manipulation, as it does not use added ingredients. Another PRF benefit lies in its flexibility and three-dimensional structure, which lead to both cytokine imprisonment and cell movement or migration. PRP, in its turn, is a fibrin condensate that renders polymers denser and turns them into a rigid network. PRF also has a receptive effect on the immune system and helps hemostasis [1]. The comparison between PRP and PRF, and their action in releasing essential growth factors for physiological actions (aimed at wound healing and tissue repair), often show these factors delivered in PRF-generated clots. These delivery factors can be observed for up to ten days, at the amount [26]. Their effects are quite similar, namely: they boost cell generation and proteins such as collagen.

The PRP/PRF confrontation is preset, and their easy generation is one of their main gains. PRP needs blood collection and the addition of a non-autogenous product, which is an artificial product used to get to the expected outcome, whereas PRF data collection is immediate [23,43]. No non-autogenous product is added to the blood after its collection when PRF is adopted. The tube is placed in the centrifuge (400 × g) for 10 minutes to prepare the product, which must be used within 4 hours after collection. When it comes to PRFM (matrix) preparation, centrifugation must be set at 1100 × g for 6 minutes; the second step is run at 4500 × g for 25 min (Figure 1) [47].

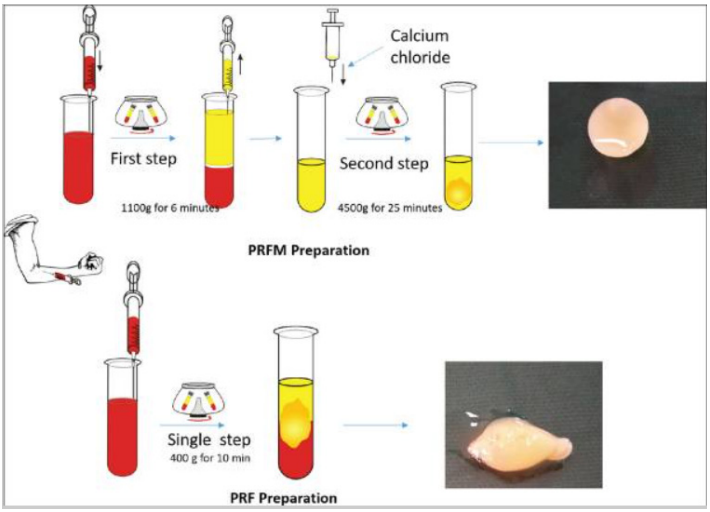

Figure 1. *Schematic diagram representing the preparation of platelet-rich fibrin (PRF) and platelet-rich fibrin matrix (PRFM) with the resultant matrix. From Nagaraja et al. [47], by permission of Wolters Kluwer Medknow under the terms of the Creative Commons Attribution Non-Commercial Share Alike 4.0 License.*

The current systematic review focused on assessing all evidence available in all medical fields about PRP efficiency in comparison with injectable platelet-rich fibrin (i-PRF). According to the conducted search, i-PRF accounted for high platelet concentrations and for a more sustained supply, besides long-term GF release in comparison with PRP over time. Research carried out in vitro showed that i-PRF remarkably improved the activity of many cell types such as skin, cartilage, bone, periodontal cells, and soft tissue cells around dental implants, as well as pulp cells. Clinical assays also recorded superior i-PRF results in skin regeneration. The i-PRF bioproduct allows a more supportive and long-lasting GF delivery. It was more advantageous in most PRP studies. It is currently acknowledged for its several medical and dental applications [3,22].

PRF for Skin Rejuvenation

The Choukroun group created a second-generation platelet concentrate known as PRF due to PRP limitations [8,9,14,15]. The group aimed at addressing some of the causes related to traditional PRP treatment. PRF means significant progress in preparation methods, since it is prepared through a single centrifugation procedure. It ruled out the need for anticoagulants and for certifying

total autologous therapy. In addition, the use of PRF in skin rejuvenation has proven to be an efficient therapy for several dermatological unrests, including facial acne scars [24], melasma [60], and wound healing post-laser ablative treatments [39,45]. Studies have highlighted its role in promoting more efficient and faster healing processes, which turned it into a promising therapeutic option in dermatology. Currently, autologous platelet concentrates have extensive application in facial rejuvenation [46,61]. They are adopted either in combination with microneedling for targeted drug delivery or integrated into mesotherapy techniques [36,39,54].

Vesala et al. assessed twelve individuals with facial wrinkles in the age group of 26-71 years [62]. The selected patients underwent three i-PRF treatment sessions at 4-week recess. Photographic documentation and clinical assessment were recorded at each session to capture patients' progression under the applied regimen. Statistical analysis was carried out to provide a better understanding of the therapeutic outcomes. A statistically notable improvement was recorded for skin elasticity and soft wrinkle reduction. None of the patients reported adverse reactions. The literature systematically informs that i-PRF remains a promising PRP alternative across various medical settings because it shows encouraging results, mainly in the dermatology field [61,62].

Comparative analysis was adopted to check the efficiency of autologous i-PRF based on microneedling versus microneedling isolation to point out atrophic acne scars [33]. A split-face study was carried out with 40 patients presenting atrophic acne scars. The right-side scar (under study) of each patient was treated with autologous i-PRF injections, and the left-side (control) scars were treated with normal saline solution - four months was the treatment time in both cases. Data assessment was carried out through the Goodman and Baron (GB) scale, based on physician subjective scores and on patient gratification or satisfaction rating. The mean baseline GB grade of each face side was recorded at 3.45 for two months. Results showed significant mean GB grade reduction in the study side (1.47) in comparison with the control side (3.33). The mean patient gratification score was quite higher for the right side (5.95) than for the left side (5.35). According to Krishnegowda et al. [33], the association between autologous asymmetry improvement correction and the natural properties of biologic fillers such as hyaluronic acid, collagen, autologous fat, PRP, and PRF has shown logical and potentially efficient possibilities for facial restoration. Autologous platelet derivatives enriched with biologically active molecules such as PDGF transform growth, i-PRF, and microneedling by synergistically improving acne scars [61].

Recently, an excellent review on PRP and PRF risks and benefits for advanced facial rejuvenation techniques was published [21]. It emphatically highlights the benefits of autologous products. This study's results are provided in the next paragraph.

Santos et al. emphasized that PRP and PRF are promising techniques with potential benefits to treat facial aging, mainly when it relates to wrinkles, hyperpigmentation, and skin texture quality [52]. Similarly, Buzalaf and Levy highlighted that PRP and PRF are safe and well-tolerated products that have an impact on facial rejuvenation by boosting collagen production, which gives the skin a more youthful appearance [6]. However, according to them, although these products may present risks, they are considered minimal, mainly in comparison with the benefits of their use. Storrer et al. mentioned the possibility of risks such as erythema, burning, and edema due to these products, but these outcomes are considered transient, lasting only 1 to 3 days [59]. They emphasize the beneficial effects of PRP and PRF for rejuvenation, mainly for skin texture and elasticity. Phoebe et al. emphasized PRP effectiveness to treat facial aging [50]. Collagen synthesis stimulation, which significantly improves skin texture and elasticity, as well as reducing wrinkles and fine lines, is among the advantages of its use. Furthermore, this product is also associated with risks such as pain, discomfort, and bruising, as well as with possible complications like infections and contamination, due to its intradermal administration. Nevertheless, according to the study, PRP is considered safe and has only recorded a few reported adverse effects. Sanz and Pinto conducted a study with PRP in combination with photothermal activation to treat facial sagging [53]. Their results have shown skin laxity decrease, which gave the skin an overall rejuvenated, smoother, and more luminous appearance. Like the previous study, this last one also reported a common risk associated with PRP application, namely: mild pain resulting from the injection. However, it reinforces that the use of this autologous product is secure and effective. The clinical trial and literature review conducted by Banihashemi et al. have proven that PRP injections for facial rejuvenation are a promising technique that presents satisfactory outcomes, mainly for dark circles and periorbital wrinkles [5]. Furthermore, it also showed improvement in nasolabial folds, and in skin quality, texture, and tone. Like the study by Santos et al. [52], this clinical trial highlighted that no serious or persistent risks were observed. Hersant et al. administered PRP and HA injections and observed that their synergistic effect enhances the benefits of the autologous component [29]. Improvements in the overall skin appearance, including texture, radiance, hydration, firmness, and elasticity, are among the benefits from collagen and elastin stimulation. However, there is a risk of adverse reactions, such as mild bruising formation, because this technique depends on injections. This risk is assumingly associated with patients' dermal fragility. Dermal strengthening was observed after the first application and subsequent cell regeneration stimulation. Chamata et al. discussed PRP benefits based on the application of different techniques such as microneedling, lasers, and intra- and subdermal injections [7]. Overall, all these procedures accounted for remarkable improvements in overall skin appearance, mainly in texture, color, wrinkles, tone, and pores. Although no serious complications were reported, this treatment can cause some adverse effects like transient edema, bruising, erythema, and discomfort. However, these authors emphasized that this technique is safe and effective for facial rejuvenation. Hu et al. carried out a comparative study on PRF injections and observed that this bioproduct's main role lies in stimulating collagen and elastin synthesis and, consequently, in working as a filler [30]. Benefits resulting from this process include skin quality and texture improvement,

and increased skin volume, smoothness, uniformity, and radiance. Therefore, PRF is considered a non-surgical facelift. According to Hassan et al., injectable PRF really favors facial rejuvenation, and its main effects comprise improved overall skin, spots, pores, texture, and wrinkle appearance [27]. Furthermore, their study did not report significant adverse effects; therefore, it was considered a safe procedure. Seoudy et al. associated PRP with CO2 laser to maximize facial aging treatment [57]. They highlighted that the PRP and laser synergistic effect leads to significant collagen synthesis stimulation, and it results in wrinkle and fine line mitigation. This technique uses an ablative laser, which can have negative effects like edema and erythema, although these are low-relevance events. Peng used PRP based on microneedling and intradermal injections to generate facial rejuvenation [49]. Both methods led to significant results; they improved wrinkle appearance, and facial texture, elasticity, tone, and volume due to collagen and elastin synthesis stimulation. However, although these procedures are minimally invasive, there are potential risks such as bruising formation. Almeida et al. combined PRP and PRF use with HA and CaHA in a clinical case report to maximize these bioproducts' benefits [2]. This technique stimulates collagen and elastin production to promote facial volumization and filling. It reduces sagging, which is a characteristic sign of facial aging.

Briefly, the use of PRP and PRF is promising for being favorable, safe, and well-tolerated to mitigate facial aging signs. Autologous products promote visible improvements in skin quality and texture, such as wrinkles and hyperpigmentation signs, due to their filling and collagen-production effects. The combination of autologous products with photothermal activation, HA, and lasers enhanced facial rejuvenation results. The same was recorded for PRF in combination with CaHA and HA. However, their use may pose risks (although rare, mild, and transient) such as allergic reactions, which can be treated without sequelae. Thus, according to the integrative review, the analyzed articles mostly emphasize PRP and PRF benefits in comparison with risks associated with facial rejuvenation procedures [21].

Fisher et al. conducted another interesting review and showed different PRF aspects. They also pointed out that there is only one publication focused on a clinical trial carried out in vivo to assess the physiological action of PRF therapies. Sclafani et al. developed restricted pilot research and presented a localized tissue feedback or response following PRF administration [56]. They found fibroblast energizing and collagen discharge before the seventh therapy day; moreover, there was significant neovascularization nineteen days after its administration. Much research has shown clinical associations with PRF's postulated action mechanism based on qualitative and quantitative skin assessments conducted to substantiate the primary results [46,55,30]. Hu et al. ran a randomized study based on a placebo-controlled trial and showed a statistically relevant VISIA score improvement in the therapeutic arm (PRFM) in comparison with the control arm three months after treatment [30].

After a long and exhausting basic investigation, Miron et al. found that liquid PRP can be produced by additionally decreasing the g force (centrifugal force) and the spinning continuation time [41]. This method was called "Injectable PRF or i-PRF or I-PRF". The spinning or centrifugal speed remains at 60 g for 3 minutes. This short centrifugation time allows separation of the possible clot formation and provides more time for clot formation, although PRF remains liquid. The volume of produced i-PRF in a 10 mL tube is 1-1.5 mL, on average. However, platelet and white blood cell (WBC) concentrations are higher than those of leukocyte-rich PRF (L-PRF). Longer spinning time can increase the number of leukocytes and platelets in the PRF, and this change is called A-PRF (Figure 2). All of these nomenclatures are justified by the fact that different centrifugation methods and times are described by different symbologies. The C-PRF, for example, is a protocol (700 g for 8 minutes) that remains liquid for 15-20 minutes before it coagulates and forms a clot. During this time, the i-PRF can be injected into the scalp or the skin of the face, or it can be mixed with bone grafting materials and molded into the required shape and clot into the desired shape [12].

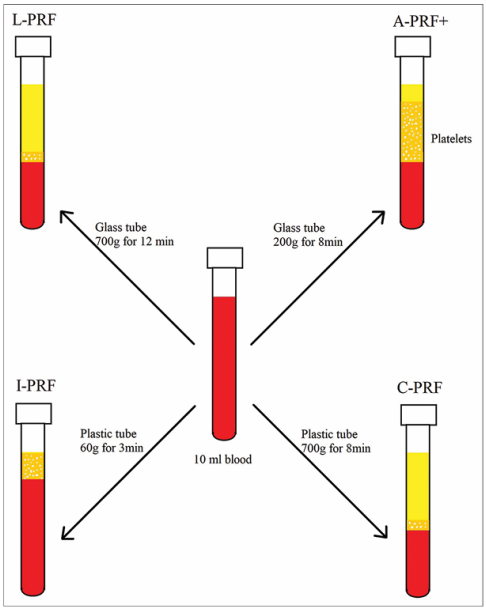

Figure 2. *Schematic representation of different types of second-generation platelet concentrates that can be prepared using different centrifugation protocols and tubes. Light yellow represents cell-free plasma; orange represents plasma containing predominantly platelets; and red represents the RBC layer. From Dashore et al. [12], with permission of Wolters Kluwer-Medknow under the terms of the Creative Commons Attribution Non-Commercial Share Alike 4.0 License.*

Monteiro et al. recently reported a practical guide for PRF production; a white or green tube is used to produce i-PRF [44]. It is featured by the lack of additives or silica, so the fibrin coagulation/polymerization time depends on the patient's own response. The tube is made of plastic because glass contains silica in its composition. Collection must be made within three minutes to prevent the coagulation process from starting, since it would stop the components from separating during the centrifugation process. After the collection is over, the tourniquet must be removed from the

patient's arm before removing the needle. The number of blood tubes (9 mL or 10 mL) can range from 4 to 8 depending on the clinical need. Choukroun® tubes sold for the PRF Process were green. The S-PRF tube can hold 10 mL of blood. The same manufacturer provides a purple tube called i-PRF+ (13 mL), which is recommended for orthopedic use and for aesthetic procedures. The upper part of the centrifugate should be aspirated with the aid of a sterile dropper or syringe with a sterile needle, right after the centrifugation procedure. The tube holding centrifuged blood can be kept in a container filled with ice (storage without agglutination for approximately 10 minutes) to delay i-PRF polymerization [44].

Protocol for Patients

What to Expect Before Your PRF Therapy Session [65]

It is necessary to meet a medical provider at any Aesthetics Center or Clinic to discuss all the concerns and goals. The aim of this consultation is to make sure that the PRF therapy will fit the patient well. Patients carrying certain health conditions or blood disorders may need alternative options; therefore, patients' complete medical history is important.

In the days before the appointment:

- Keep well hydrated;
- Prevent alcohol intake and smoking;
- Avoid taking blood-thinning medications.

Being well rested and hydrated ensures a smooth procedure and high-quality blood for PRF administration.

What Happens During the PRF Therapy

The technique itself is quite fast and negligibly invasive. There are some aspects to be considered:

1. Blood harvest: A little amount of blood is lost due to routine lab procedures.
2. Centrifugation: The blood is rapidly centrifuged to separate the PRF from the other elements.
3. Preparation: Product generation depends on the procedure plan - PRF is administrated right away.
4. Application: The medical staff or provider administrates the PRF into specific areas.

All these procedures often take approximately 45-60 minutes. Most individuals only feel mild discomfort. A topical anesthetic cream can be applied if the patient is sensitive to pain.

What to Expect After the PRF or PRF Therapy

Patients can return to almost all normal activities on the day after the PRF therapy session; however, the targeted areas may have little swelling, rosiness, or painfulness. Overall, these secondary effects vanish within a few days.

There are some post-care suggestions to take into consideration, namely:

- Refrain from touching or manipulating the targeted areas;
- Refrain from makeup and/or other skincare over the first days after the session;
- Refrain from sun exposure, enforced workouts, or extreme temperature environments for 3-4 days;
- Follow all specific care demands described by the medical staff or provider.

Assumingly, the benefits of PRF administration feature the minimal downtime possible. It is expected to feel subtle improvements within a few days; full-information outcomes slowly come up over the weeks as collagen is replenished.

Interestingly, many patients find immediate volume improvement after PRF, and the skin keeps on improving after some growth factor delivery time.

Legal and Ethical Aspects of PRP or PRF

Informed consent must be read and signed by the patients, as described by Codorean et al. [11]. An example of it is available in the WRS Health PRP Consent Form, and another example is available in the PRP Health General Consent Form.

Conclusion

PRP is a feasible alternative for skin recuperation, but PRF shows new updates due to its fibrin matrix and controlled GF release. According to these findings, PRF, including CGF, may become an alternative for long-term therapies that require stronger and more substantial production. A systematic review of evidence available in all medical fields about PRP and i-PRF shows that i-PRF produced higher platelet concentrations and provided more sustained and long-term GF releases in comparison with PRP [3,22]. Studies conducted in vitro have shown that i-PRF significantly improves the function of many cell types, including skin and cartilage cells. Clinical trials have shown that i-PRF leads to superior skin regeneration outcomes than PRP, and it is currently acknowledged for its application in several medical and dermatological uses [3,22]. In addition to the properties and to its use in skin rejuvenation, PRF has been proven efficient in treating several dermatological conditions, including facial acne scars, melasma, and scarring, among others [24,39,45,60]. Besides its fast-healing properties, which have turned it into a promising therapeutic option in dermatology, studies have also related autologous platelets to wide application methods for facial rejuvenation [46,61]. Different publications described the i-PRF preparation, and standard preparation was specified: low and fast centrifugation (60 × g for 3 min) [41]. It remains liquid for 15-20 min before coagulating to form a clot. During this time, the i-PRF can be injected into the scalp or the skin of the face [12]. Finally, many aspects related to safety and specialists' ethical behavior are extremely important. The therapy must be preceded by an informed consent form signed by the patient [11].

Author Contributions

GD and ND contributed to formal analysis, investigation, methodology, supervision, validation, visualization, data collection and analysis, writing of the original draft, and final editing of the manuscript.

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Conflicts of Interest

The authors declare that they have no conflicts of interest.

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