Platelet-Rich Fibrin Matrix for Facial Plastic Surgery

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**KEYWORDS**

- Platelet-rich fibrin matrix (PRFM)
- Platelet-rich plasma (PRP)
- Platelets
- Wound healing
- Collagen
- Angiogenesis
- Adipogenesis

**Key Points**

Platelet-rich plasma (PRP) has been used clinically to simulate the native wound healing environment, but surgeons are cautioned not to generalize reported results; although many are approved by the US Food and Drug Administration, these preparations may vary greatly in erythrocyte contamination, leukocyte content, method of activation, and volume.

Platelet-rich fibrinogen matrix (PRFM) is a better product than PRP for use in facial plastic surgery because:

- The action of PRFM is more steady and sustained, yielding increased and sustained concentrations of growth factors during the crucial wound healing period after the initial acute inflammatory phase.
- The mechanical properties of PRFM, once fully polymerized, are significantly more stiff, representing a stiffness about half that of intact human skin.
- The robust scaffolding structure of PRFM possibly translates into resistance to physiologic stress, more accurate implantation, and presumably longer persistence and resistance to washout at the site of injection.

**INTRODUCTION**

Platelets play a major role in hemostasis, but their functions in regulation of immune response, wound healing, osteogenesis, and angiogenesis have only recently become the subject of extensive investigation.\textsuperscript{1–3}

In vivo, activation of platelets is mediated by contact with the site of injury and attachment to the fibrin scaffolding formed at the site of injury, with subsequent biochemical cascades that lead to, among other effects, pseudopod formation, aggregation, and degranulation of platelets. Derived from megakaryocytes, platelets store bioactive molecules in their secretory organelles. \(\alpha\)-Granules contain more than 300 proteins, many of which are yet to be characterized.\textsuperscript{4} These proteins are involved in many biologic roles including hemostasis

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and clotting, cell proliferation, extracellular matrix formation, angiogenesis, vascular modeling, chemotaxis, and inflammation. The complex interaction of these molecules with cells involved in wound repair, such as fibroblasts, macrophages, and endothelial cells, is central to understanding wound repair.

Some of the proteins released from $\alpha$-granules of activated platelets are specifically involved in wound healing, including tumor growth factor $\beta$ (TGF-$\beta$), platelet-derived growth factor (PDGF), insulinlike growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), and connective tissue growth factor (CTGF). In addition, platelets release coagulation factors, serotonin, histamine, endostatin, and hydrolytic enzymes. As noted earlier, activation of platelets is mediated by contact with the site of injury and leads to the release of bioactive substances from platelets (mentioned earlier). The complex interaction of these molecules with cells involved in wound repair, such as fibroblasts, macrophages, and endothelial cells, is central to wound repair.

Growth factors are released in exact ratios and work in specific order, both independently and in concert, to lead to appropriate hemostasis, inflammation, and wound healing.

THE USE OF EXOGENOUS GROWTH FACTORS

Therapeutically modifying the amount of these bioactive substances, and thus enhancing wound healing, is useful to the scientist and clinician. Pharmacologic agents such as human recombinant PDGF (becaplermin 0.01%, Regranex; Systa-genix Wound Management, Inc., London, United Kingdom), in use for diabetic foot ulcers, and human recombinant keratinocyte growth factor used for oral mucositis in patients receiving chemotherapy (palifermin, Kepivance; Biovitrum AB, Stockholm, Sweden) have been formulated, studied, and shown to be effective.

In light of the abundance of bioactive chemicals in platelets and the complexity of their interactions and effects, studies of the application of single growth factors have not produced uniform or conclusive clinical results. In addition, exogenous growth factor application directly and outside a natural site of healing may have untoward effects: in 2008, the US Food and Drug Administration (FDA) issued a black box warning for the use of becaplermin, because patients exposed to 3 or more tubes of this drug had a 5-fold increase in cancer mortality. The safety of palifermin in patients with nonhematologic malignancies has not been established. However, if platelets can effectively be delivered to the site of injury, improved and accelerated healing may be expected.

USE OF ENDOGENOUS PLATELETS

To better simulate the native wound healing environment, concentrated platelet preparations (PRP) have been used clinically. There are several FDA-approved systems to produce a PRP, but their products vary in erythrocyte contamination, leukocyte content, method of activation, and volume, and the reader is cautioned not to overly generalize reported results from PRP.

Platelet Preparations

Autologous blood is centrifuged followed by resuspension of platelets in a small amount of recovered plasma after erythrocytes and leukocytes are removed. This process yields a PRP with 3 to 5 times the normal concentration of platelets in peripheral blood. The PRP is then usually activated with calcium and bovine thrombin, which leads to platelet degranulation and massive release of all growth factors. Depending on the system used, some PRP preparations also contain leukocytes (predominantly lymphocytes); although there is some indication that leukocytes may enhance the antibacterial activity of PRP, they may be counterproductive in inducing tissue generation, because they are also known to release matrix metalloproteins and reactive oxygen species.

Surgeons in varied disciplines have used PRP to modulate wound healing, including attempts at accelerating the healing of bone grafts in orthopedic and sports medicine, as recently reviewed by Nguyen and colleagues and in the dental literature. PRP has also been used for improved healing of chronic lower extremity wounds and progressive hemifacial atrophy. Man and colleagues described the use of PRP in 20 patients undergoing cosmetic surgery including neck lift, face lift, breast augmentation, and breast reduction. Cervelli and colleagues reviewed the use of PRP in conjunction with fat grafting in several aesthetic and reconstructive procedures.

Clinical results reported with the use of PRP have been equivocal, possibly because most growth factors, such as TGF-$\beta$ and PDGF, are released immediately from the PRP platelets, with significant reductions at days 3, 7, and 14. This finding may explain the transient effect of PRP on wound healing. In an animal study, Sclafani and colleagues noted an increase at day 7 in endothelial cells and fibroblasts after application of PRP to experimental wounds; however, this increase was lost by day 14. In a different
experiment, Horn and colleagues\textsuperscript{23} used autologous platelet gel to treat wounds of the adult thigh, and although earlier wound epithelialization was noted with the use of the gel, ultimate cellularity was comparable with that of controls. This finding is supported by the work of other investigators, who found the effect of exogenous epidermal growth factor (EGF) application to be transient, and that only sustained application of EGF improved wound healing.\textsuperscript{24}

In their study comparing hemifaces treated with PRP before flap closure during deep-plane face-lifts, Powell and colleagues\textsuperscript{25} did not note a significant difference in postoperative edema and ecchymosis compared with control hemifaces. Others failed to show any significant improvement with the clinical use of PRP in a randomized clinical study.\textsuperscript{26}

**Platelet-Rich Fibrin Matrix**

In addition to platelets and their products, the natural wound response requires the presence of a fibrin matrix, which enhances the delivery of growth factors.\textsuperscript{27} Fibrin mediates the adhesion of fibroblasts and other cells to the injured site.\textsuperscript{28} Furthermore, basic fibroblast growth factor (bFGF) has a high binding affinity specifically for fibrin and fibrinogen.\textsuperscript{29} Studies have shown enhanced survival and differentiation of transplanted preadipocytes when coinjected with fibrin as a carrier material compared with controls.\textsuperscript{30,31} Other clinical studies have reported good results when treating patients with autologous fat coinjected with PRFM.\textsuperscript{32,33}

Animal studies have also suggested improved wound healing when PRFM is used. Nitche and colleagues\textsuperscript{34} found that rabbit patellar tendon defects treated with surgery had more desirable wound healing when additionally treated with PRFM compared with surgical repair alone. This finding was quantified by decreased inflammation, more organized collagen deposition, and increased tensile strength at 3 weeks. This difference was not noticed at 6 weeks after surgery. In a different study, Sanchez and colleagues\textsuperscript{35} postoperative application of PRFM after Achilles tendon repair significantly improved recovery time and time to full range of motion. PRFM has also been used to improve the healing of chronic venous leg ulcers.\textsuperscript{36}

In the dental literature, a study by Choukroun and colleagues\textsuperscript{37} suggested that patients undergoing sinus floor augmentation showed significantly accelerated healing and bone regeneration when the bone allograft used was combined with platelet-rich fibrin, compared with those in whom bone allograft alone was used.

**PRP VERSUS PRFM IN FACIAL PLASTIC SURGERY**

Several factors make PRFM a better product than PRP for use in facial plastic surgery. As mentioned earlier, PRP releases growth factors mainly in the first day. In contrast, the action of PRFM is more steady and sustained, yielding increased and sustained concentrations of growth factors during the more crucial time of wound healing after the initial acute inflammatory phase. It is suggested that the natural fibrin framework in PRFM protects the growth factors from proteolysis,\textsuperscript{38} which may contribute to this finding. Another contributing factor may be the mechanical properties of PRFM compared with PRP. Although conventional PRPs are usually thin liquids or weakly gelatinous and prone to rapid proteolysis, PRFM, once fully polymerized, is significantly more stiff, with an elastic modulus of approximately 937.3 kPa, as cited by Lucarelli and colleagues,\textsuperscript{39} which represents a stiffness about half that of intact human skin.\textsuperscript{39,40}

The senior author injects PRFM before the fibrin mesh is fully formed, allowing this process to occur in situ. Once the fibrin mesh forms, it may produce a more robust scaffolding structure for wound repair. It is possible that this robustness translates into more resistance to physiologic stress, more accurate implantation, and presumably longer persistence and resistance to washout at the site of injection.

**SELPHYL PRFM THERAPY**

The senior author uses the FDA-cleared device, Selphyl (Aesthetic Factors, LLC, Wayne, NJ, USA) to produce an autologous PRFM. Peripheral blood is drawn from the patient into a vacuum collection tube containing a thixotropic separator gel. This tube is centrifuged for 6 minutes at 1100 rpm, which yields a supernatant plasma/platelet suspension and the cellular components (erythrocytes and leukocytes) below the separator gel (Fig. 1). The plasma/platelet suspension is transferred to a second vacuum tube containing calcium chloride, which initiates the polymerization of fibrin. This polymerization process is completed in about 10 to 12 minutes (Fig. 2) and the platelet-rich fibrin matrix can be injected through a 30-gauge needle before full polymerization. These platelets, embedded in the fibrin matrix, are capable of sustained release of PDGF, VEGF, TGF-B, and IGF-1 over 7 days.\textsuperscript{39}

In a clinical study, Sclafani\textsuperscript{41} showed that a single injection of PRFM below deep nasolabial folds could improve most moderate to deep nasolabial folds. The improvement was statistically
significant within 14 days of treatment, and was stable for the remainder of the 3-month study. Sclafani later reported on his clinical experience with PRFM for facial uses, finding PRFM to be efficacious and well tolerated. Most patients required multiple treatments for optimal effect.

More recently, Sclafani and McCormick reported on the histologic changes associated with injection of PRFM into the dermis and subdermis in human skin. These investigators found significant new collagen deposition as early as 7 days, and significant angioneogenesis and adipogenesis clearly present by 19 days, without any evidence of cellular atypia.

CLINICAL USES OF PRFM

The following techniques have been developed and used by the senior author (APS) for several years. They have undergone several modifications over time to achieve the most desirable results.

The hemostatic, fibrogenic, and angiogenic properties of PRFM have been used in procedures such as rhytidectomy, rhinoplasty, and facial implants, in which rapid healing, minimal edema, and reduction of ecchymosis are desired.

Because of its angiogenic abilities, PRFM has been coinjected during autologous fat transfer to enhance the viability and survival of the fat. Evidence from the work of Sclafani and McCormick suggests that PRFM can also induce an anabolic state in mature fat as well as potentially promoting more rapid vascularization of the transferred fat (Fig. 3).

TREATMENT TECHNIQUES

After properly assessing the patients’ needs and desires, the optimal amount of PRFM is determined (Video 1). Typically, the application of topical anesthetic for most treatments provides adequate anesthesia. However, infiltration of local anesthetic may be required in some cases depending on patient discomfort levels. The amount of PRFM needed for each treatment depends on the individual patient anatomy.

After treatment, intermittent application of cool compresses to the injected areas for the first few hours decreases discomfort, bruising, and swelling. Massaging the area the first several hours may cause washout of the PRFM and should be avoided.
to 25% overcorrection is desired, which generally subsides within 4 to 8 hours.

**Treatment of Tear Troughs and Suborbital Hollows**

A 27-gauge needle is advanced through the skin along the area of suborbital volume deficiency. Careful linear retrograde injection of PRFM below and above the orbicularis oculi muscle is performed to achieve a smooth and even volume augmentation. Tear troughs are typically treated with 0.75 to 1.00 mL, whereas the remaining suborbital hollow requires about 1.00 mL (Fig. 4).

**Glabellar Furrows**

Glabellar furrows may be spread apart using the nondominant hand while each individual wrinkle is intradermally injected with PRFM using a 30-gauge needle. Once the rhytids are effaced, additional PRFM may be injected subdermally for volume augmentation. Treatment of a typically glabella requires 0.50 to 0.75 mL. Slight overcorrection is desirable. It is essential to avoid intravascular injection.

**MIDFACE AND LOWER FACE TREATMENTS**

**Malar Augmentation**

A single treatment typically requires 1.50 to 2.50 mL of PRFM per side. A 27-gauge needle is advanced through the skin and into the malar fat pad. Injection of PRFM is performed linearly in a fan pattern as the needle is withdrawn, depositing PRFM within the malar fat as well as in the immediate subdermis.

**Zygomatic Arch Enhancement**

A single treatment per side typically requires 1 to 1.75 mL of PRFM. The needle is advanced through the skin and parallel to the zygomatic arch in a
subcutaneous plane. Linear aliquots of PRFM are then injected as the needle is withdrawn.

**Correction of Nasolabial and Marionette Folds**

A 27-gauge or 30-gauge needle is used to inject PRFM into the desired areas at the dermal-subdermal layer in a fanlike pattern. In the case of marionette folds, injection should ideally be limited to a triangular area with its base along the white roll of the lower lip. Injection lateral to the depressed area should be avoided. Overcorrection by 20% to 25% is desired. Typical volumes of PRFM used are 1.50 to 2.00 mL for nasolabial folds and 0.75 to 1.25 mL for marionette folds, per side (Figs. 5 and 6).

Similar techniques may be used to treat perioral rhytids, prejowl folds, or other desired areas.

**Treatment of Rolling Acne Scars and Boxcar Acne Scars**

A modified subcision technique is used. A 21-gauge needle is passed through the skin and advanced at the dermal-subdermal layer until the tip rests below the site to be corrected. The sharp edge of the needle bevel is then swept from side to side to sharply divide the subdermal scar tissue tethering the acne scars. This subcision generally

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**Fig. 5.** Patient treated once with PRFM in the nasolabial folds before (left) and 3 months after (right) treatment.

**Fig. 6.** Patient treated once with PRFM in the nasolabial folds only (A) and 12 months after (B) treatment.
meets less resistance in boxcar acne scars. PRFM is then injected in a fan pattern into the potential space created at the desired site. Another needle entry site is then used to create a crosshatched pattern of threads of dermal-subdermal augmentation. Again, overcorrection is desirable, because the plasma is quickly absorbed. The volume of PRFM used varies based on the area of acne scarring to be treated, but 2 to 2.50 mL are typical for acne scarring in the cheek. If necessary, treatment may be repeated in 4 to 6 weeks (Fig. 7).

After soft tissue injections, for most areas, the window of partial volume loss between the absorption of the plasma and noticeable neocollagenesis, typically lasts 1 to 2 weeks. After this period, new collagen formed in the injected areas maintains correction of the rhytids. If necessary, additional volume correction treatment may be performed 4 to 6 weeks after the initial injection.

**Enhancing Autologous Fat Transfer Results With PRFM**

After assessing the amount of transfer required based on the patient’s needs and desires, autologous fat is harvested and purified using the technique described by Coleman. The centrifuged fat is then mixed with PRFM in a 2:1 ratio. Two milliliters of fat are transferred to a 5-mL syringe, to which 1 mL of PRFM is added (Fig. 8). The contents of the syringe are then mixed by gently passing them back and forth between two 5-mL syringes several times. The mixture is then transferred to separate 1-mL syringes for use.

The fat/PRFM mixture can then be placed in desired areas using stab incisions placed at distances from the deposit site. The incisions are then closed using 5-0 chromic sutures. Overcorrection by 20% to 25% is desired.
The typical amount of PRFM used in a facelift is about 2 mL per side. After the superficial muscular aponeurotic system (SMAS) modification and re-draping of the skin, PRFM is uniformly delivered from a 3-mL syringe via a plastic angiocatheter placed under the skin flap as distally as possible. Excess fluid is then rolled out and skin is closed in the usual fashion. No drain is used, and a compressive facelift dressing is placed.

Using a 21-gauge needle, 2 mL/side PRFM may be injected during rhinoplasty along the osteotomy lines, immediately after withdrawing the osteotome (Fig. 9).

After placement of a malar or chin implant, the implant surface can be coated with approximately 2.0 mL of PRFM to promote rapid integration of the implant into the surrounding tissues.

### SUMMARY

Autologous PRFM allows the surgeon to directly deliver a concentrated and functional wound healing response to a target area, which can enhance the patient’s natural wound healing ability. In the absence of a wound, PRFM can stimulate the production of viable blood vessels, fat cells, and collagen deposits that seem to persist over time. PRFM does not replace good technique and sound medical judgment, but may assist in guiding tissue generation in areas of interest. PRFM fundamentally differs from other PRP systems in that it promotes the physiologic functions of fibrin and avoids the potential drawbacks of included leukocytes. PRFM must rely on the local tissues’ ability to generate a cellular response, and may not be as effective in unfavorable wound conditions such as hypoxia or infection. However, PRFM is a significant new tool during minimally invasive procedures.

### NOTES FOR EARLY USERS

- After centrifugation, gently invert the tube 10 times to fully resuspend the platelets in the plasma. This step is essential to maximize platelet yield.
- Once activated by calcium in the second tube, PRFM begins to undergo fibrin polymerization. After 10 to 12 minutes, it is no longer possible to inject PRFM. If using multiple tubes, activate only 1 at a time to avoid polymerization before use.
- Patients should understand that multiple treatments are often required.
- After injection, correction initially subsides as plasma is resorbed. This loss of correction generally plateaus between 1 and 3 weeks, and the remaining correction is fairly stable over the long term.
- Patients must understand that the correction obtained is based on the response of their soft tissues. Hence, patients who require substantial volume augmentation or who desire an immediate result may not be good candidates for PRFM.
- A small percentage (10% or less) of patients do not generate a tissue response sufficient to produce a clinically acceptable result.

**Fig. 9.** Injection of PRFM immediately after performing lateral osteotomies may help reduce postoperative ecchymosis and edema. Before (A) and 1 week (B), 3 weeks (C), and 10 weeks (D) after surgery.
invasive as well as open surgical procedures. Work is currently underway to investigate other potential clinical uses for PRFM.

REFERENCES


