

The Benefits of Platelet-Rich Fibrin



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KEYWORDS

- Autologous • Fibrin • Grafting • Platelet • Natural filler • Regenerative therapy • Rejuvenation
- Stem cell

KEY POINTS

- PRF is similar to PRP except that PRF naturally contains fibrin for clot scaffolding and localization of mesenchymal stem cells.
- PRF formation and centrifugation differs from PRP in that there is no anticoagulant and spin times and speeds differ.
- PRF has implied use as a natural filler.
- PRF has had remarked success as a complementary component in surgical and nonsurgical esthetic treatments.
- PRF releases platelet-related therapeutic granules for a longer duration and at a slower rate than PRP.



Video content accompanies this article at <http://www.facialplastic.theclinics.com>.

A NEW FRONT IN MEDICAL THERAPIES

Wound healing and tissue regeneration are fundamental goals of medical care. In this context, the use of autologous blood concentrates has emerged. Historically, the primary use of such therapy was in oral maxillofacial surgery;¹ however, its use in surgical and noninvasive esthetic procedures has shown notable success, suggesting a bright future for esthetic and reconstructive medicine.

Autologous platelet therapy gained popularity in the 1990s with the use of platelet-rich plasma (PRP), which has since found several medical applications. The focus of this article is the next generation of autologous blood concentrate therapy, platelet-rich fibrin (PRF), and its roles in esthetic medicine. The significance of these developments will become apparent throughout the review of the composition of whole blood.

WHOLE BLOOD COMPOSITION

Blood is composed of plasma (55%) and cells (45%).² Plasma consists mostly of water (92%), as well as soluble proteins, electrolytes, and metabolic wastes. The most notable soluble constituent is fibrinogen, a clotting protein. When tissue and vascular injury occur, thrombin enzymatically converts fibrinogen to insoluble fibrin.^{2–5} Fibrin then acts as the binding scaffold for platelets and erythrocytes in clot formation, which is the essential first step in wound healing and tissue regeneration.^{1–4} Beyond plasma, red blood cells (erythrocytes), white blood cells (leukocytes), and platelets (thrombocytes) constitute the remaining cellular component of whole blood.² Erythrocytes are the most abundant, comprising about 44% of total blood composition, whereas leukocytes and thrombocytes constitute the buffy coat at less than 1%.²

Disclosure Statement: Dr K. Karimi is the medical director of CosmoFrance, which manufactures and distributes PRF centrifuges and tubes. H. Rockwell has nothing to disclose.

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Facial Plast Surg Clin N Am 27 (2019) 331–340

<https://doi.org/10.1016/j.fsc.2019.03.005>

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Centrifuging whole blood conveniently separates its components according to density. Erythrocytes collect at the bottom of the tube, forming the hematocrit layer; the thin, white-tinted buffy coat settles at the top of the erythrocytes; and plasma forms the supernatant.^{1,2,6} Varying centrifugation speed and duration further separates blood concentrate components. Anticoagulants or enzymatic supplements may be required to separate PRP and platelet-poor plasma (PPP),^{1,7} the former with enough platelets for therapeutic use, yet less abundant than PPP at roughly 25% and 75% of the supernatant volume, respectively.⁸

WHAT IS AUTOLOGOUS BLOOD CONCENTRATE THERAPY?

First, There Was PRP

The widely accepted mechanism of PRP therapy is growth factor secretion from platelet alpha granules. When activated in vivo through injury and clot formation, alpha factors bind to the platelet surface and release platelet-derived growth factors, transforming growth factors, fibroblastic growth factor, epithelial cell growth factor, insulin-like growth factor, and vascular endothelial growth factor (**Table 1**).^{1,8-10} Collectively, these signals

help stimulate mesenchymal stem cell (MSC) migration and differentiation at the site of clot formation.^{1,11,12} For PRP, induced clot formation localizes growth factor secretion to its implemented site.^{1,13}

In aging skin, PRP's targeted growth factor secretion promotes fibroblast proliferation and gene expression that stimulates type I collagenesis.¹⁴ To harness these abilities, PRP must first be produced using anticoagulant.^{6,10} Second, to ensure that platelet activation and fibrin clot formation occurs, calcium chloride and thrombin, which is often bovine derived,⁶ must be added to the PRP preparation^{6,9,10,13,15}; using bovine-derived thrombin poses the risk of inducing adverse immunologic reactions.^{6,16} Alternatively, additives can be omitted and trust that activation and clot formation occur spontaneously in vivo,¹³ which is not guaranteed. If PRP's production process potentially compromises its benefits, then its antiaging properties may also be at risk. Fortunately, PRF is a readily available promising alternative.

The Next Generation of Autologous Platelet Therapy: Platelet Rich Fibrin

PRF was first introduced in 2000 by Joseph Choukroun and colleagues.¹⁷ PRF offers all the clinical benefits of PRP as well as a naturally forming fibrin scaffold that guides clot formation, serves as a supportive template for tissue regeneration, and that sustains growth factors and stem cells.^{6,10,18}

In contrast to PRP, PRF is obtained by centrifuging whole blood without any additives.^{10,15} Without anticoagulant, PRF spontaneously forms a fibrin matrix gelatinous clot^{9,10,15} that confines growth factor secretion to the clotting site. In tissue repair, recruited fibroblasts reorganize this fibrin matrix and initiate collagen synthesis.¹⁹ Thus, the combined effects of growth factor secretion and fibroblast recruitment in PRF work synergistically to promote collagenesis and tissue regeneration.

Injury-induced growth factor signaling recruits MSCs to the compromised site^{11,12,20,21} where they subsequently differentiate.^{11,18,21} Surgeries and injections simulate local injury and trigger the same signaling cascade. Applying PRF with these treatments localizes and enhances the regenerative processes spurred by the body's natural response to injury. In the context of attracting, entrapping, and sustaining MSCs, research has also revealed that fibrin serves as a successful culture medium and carrier of MSCs,^{18,22,23} which preserves the paracrine functions essential in conferring their regenerative effects.²⁴

Table 1
Platelet therapy growth factor functions

Platelet-derived growth factor (PDGF α , PDGF β , PDGF γ)	<ul style="list-style-type: none"> • Triggers the activities of neutrophils, fibroblasts, and macrophages • Chemoattractant/cell proliferator • Stimulates mesenchymal cell lineages
Transforming growth factor (TGF β 1, TGF β 2, TGF β 3)	<ul style="list-style-type: none"> • Promotes cellular differentiation and replication • Stimulates matrix and collagen synthesis • Stimulates fibroblast activity and collagen production
Vascular endothelial growth factor (VEGF)	<ul style="list-style-type: none"> • Angiogenesis • Stimulates synthesis of basal lamina
Fibroblastic growth factor (FGF)	<ul style="list-style-type: none"> • Angiogenesis • Fibroblast production
Epithelial cell growth factor (ECGF)	<ul style="list-style-type: none"> • Stimulates epithelial cell replication
Insulin-like growth factor (IGF-1)	<ul style="list-style-type: none"> • Promotes cellular growth and proliferation

PRF also sustains other vital cells, including leukocytes.¹⁸ Analyzing the cellular content of the PRF clot reveals that most leukocytes within a whole-blood sample are contained within PRF after centrifugation.^{10,25} These leukocytes secrete signaling factors that further stimulate tissue repair^{1,26} and MSC recruitment.¹²

MSCs bear important regenerative applications; their multipotency allows them to give rise to several tissues including bone, cartilage, adipose, dermis, and other mesodermal tissues.^{27–29} MSCs in peripheral blood have been isolated^{30,31} and shown to proliferate and differentiate on stimulation.^{21,32} Di Liddo and colleagues³³ detected in vitro multipotent stem cell markers within PRF, and reported that a fraction of cells in PRF express defining phenotypic features of MSCs. Therefore, PRF establishes a local environment conducive to MSC migration and may also serve as a stem cell source.

Altering centrifugation duration and speed allows for manipulation of product volume and clotting onset. Broadly, this yields 2 categories of PRF:

1. Injectable PRF: clot formation occurs around 15 minutes postcentrifugation³⁴

2. PRF that coagulates during centrifugation: this is most useful when a biological membrane or a physiologic glue is needed (**Fig. 1**)

Platelet-Rich Plasma Versus Platelet Rich Fibrin

PRF has various advantages over PRP. With PRP and other past-generation platelet concentrates, growth factor release is initially rapid, yielding short-lived, early healing benefits without long-term improvement.¹⁵ The relatively short half-lives of growth factors,^{13,35} in conjunction with their abundant and rapid release following PRP activation,³⁶ supports this lack of prolonged efficacy, because tissue receptor saturation may prevent additional growth factors from binding a receptor before their degradation.¹³ Recall that preparing functional PRP requires external additives, which brings uncertainty about its spontaneous activation in vivo. Thus, functional PRP is either nonautologous, or its efficacy is unguaranteed.

Contrastingly, PRF requires no additives. Activation and fibrin clot formation are based on known, intrinsic properties of blood, and the timeliness of activation is relatively well understood.

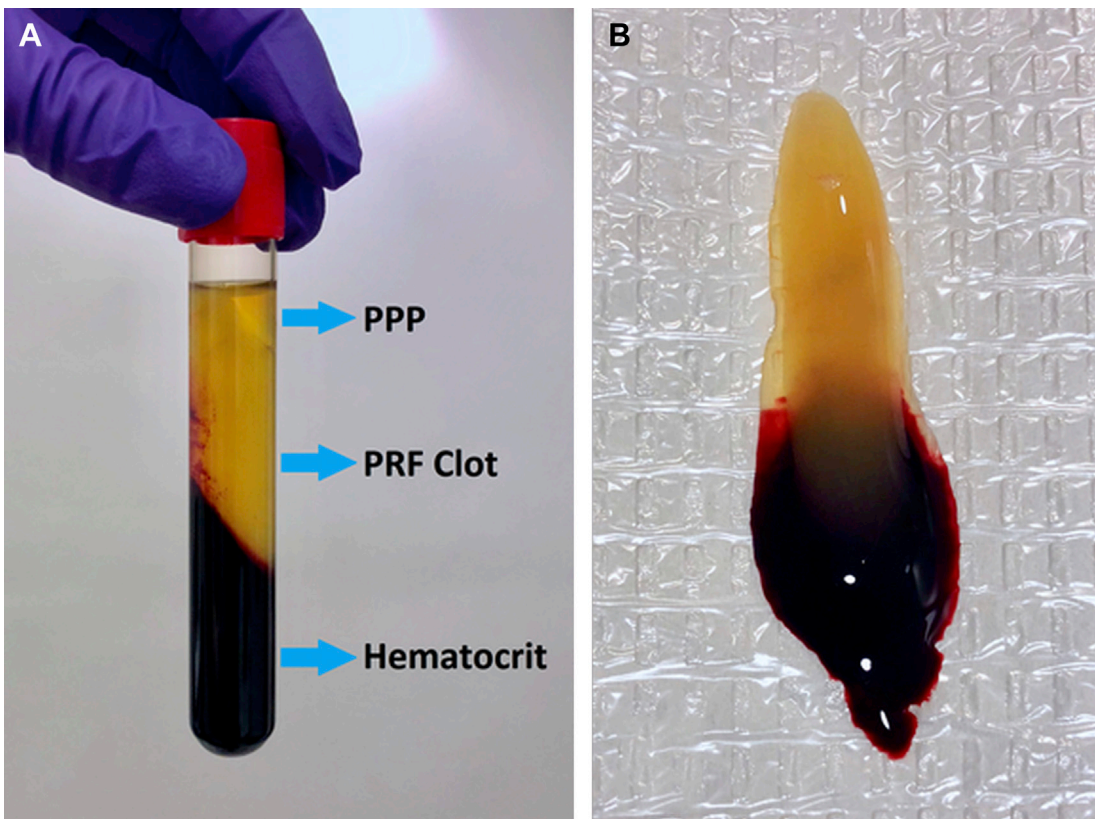


Fig. 1. (A) Visualization of the resulting blood concentrate layers from centrifugation to immediately procure a PRF clot. (B) The PRF clot removed from the centrifuge tube.

Furthermore, the holistically autologous nature of PRF reduces the risk of immunogenic reaction and disease transmission.⁶

Most notably, in comparison with PRP's rapid growth factor release, PRF releases growth factors for an extended duration of time: up to 7 days for most growth factors,¹⁵ and even longer for others.³⁷ It is proposed that PRF's composition aids in preventing rapid proteolysis of growth factors,³⁸ thereby enabling prolonged secretion. In addition, the slow polymerization and remodeling of the fibrin matrix within PRF, compared with PRP's more rapid, haphazard polymerization, effectively sustains growth factors and other critical cells.^{7,9,15} Masuki and colleagues³⁹ concluded from their comparative analysis that growth factor concentrations are generally higher in PRF than PRP, a finding that supports PRF's marked efficacy in stimulating angiogenesis, wound healing, and tissue regeneration. As previously mentioned, growth factors chemotactically attract MSCs. Therefore, it is reasonably assumed that PRF's sustained growth factor secretion, in comparison with PRP, more strongly induces MSC migration to the site of its application, a conclusion that is further backed by comparative in vitro studies.^{37,40}

Beyond their chemotactic and compositional differences, PRF and PRP undergo different centrifugation premises for their procurement (**Fig. 2**). The low-speed centrifugation of PRF tends to better preserve the beneficial cellular content within the resulting PRF layer,^{26,34,41} whereas high-speed centrifugation, such as that seen in the hardspin stage of PRP preparation,¹⁰ tends to push most cells to the bottom of the tube.²⁶

Regarding cost, PRP incurs the cost of separating gel, anticoagulant, and activation additives, whereas PRF does not. PRF use implies reduced costs for provider and patient alike.

APPLICATIONS OF PLATELET RICH FIBRIN

The following text outlines a few of the many applications of PRF in cosmetic medicine and surgery. Other applications not discussed, but worth mentioning, include enhanced healing following ablative skin resurfacing laser treatments and collagen induction with microneedling.

Natural Filler

Aging skin naturally loses collagen, elasticity, and volume. The dermis thins and the fibroblast

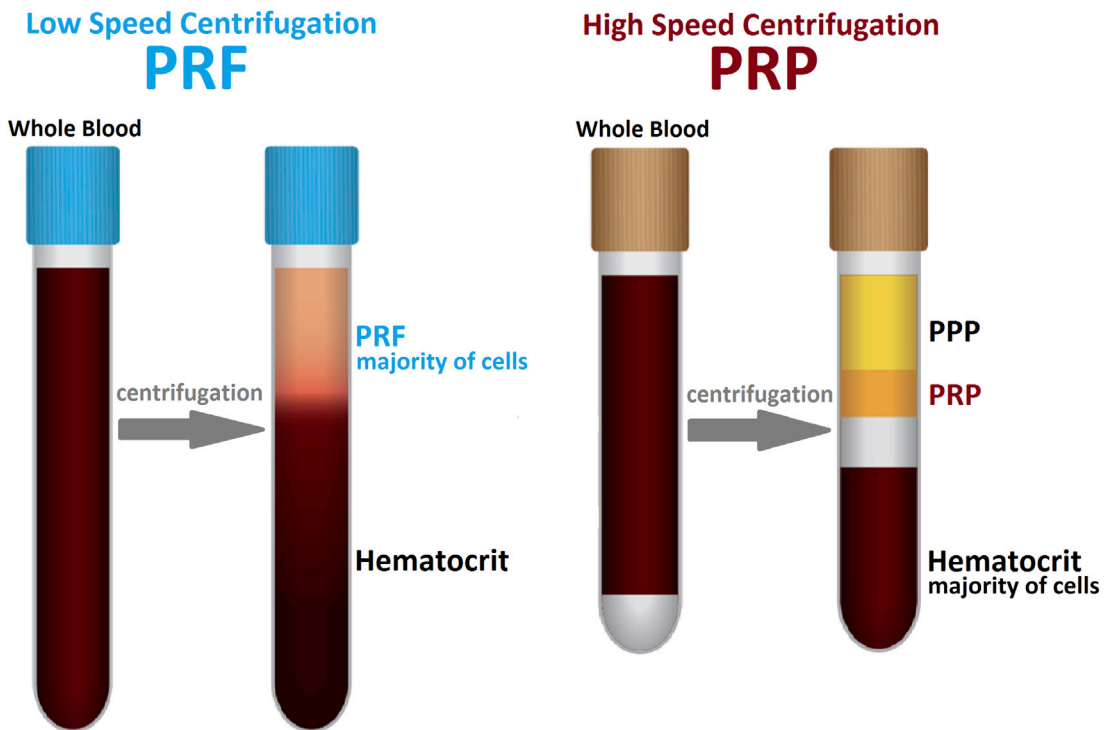


Fig. 2. Separations achieved by each blood concentrates' respective centrifugation parameters. The white separating gel and anticoagulant necessary for preparing PRP is visualized at the bottom of the whole blood tube and is pictured separating PRP and the hematocrit in the PRP postcentrifugation tube. (Courtesy of CosmoFrance, Inc., Miami, FL.)

population declines, reducing the production of collagen and hyaluronic acid.⁴² As collagen decreases by approximately 1% yearly,⁴³ skin laxity and wrinkling become apparent.^{14,43} Our skin also loses moisture because the hydrophilic hyaluronic acid concentration declines.⁴⁴ Consequently, the dermis loses turgidity,⁴⁵ resulting in volume loss and unesthetic changes. Stimulating collagenesis and hyaluronic acid content within aging skin may overcome these changes. Here, PRF shows promise.

With high concentrations and slow release of fibroblastic growth factors, PRF, when injected beneath the skin, should stimulate fibroblast formation and subsequently increase collagen and hyaluronic acid content. PRF also enmeshes hyaluronic acid, sustaining it where injected.⁷ As it forms a gel, PRF produces an immediate volumization effect; although this volumization lasts only a few weeks, repeated treatments yield long-term effects from prolonged collagen production and localized regenerative activity.

In his own practice, the primary author has found success with injecting PRF alone as a natural, autologous dermal filler, which has resulted in volume restoration of hollowing tear troughs, improved fine lines, and homogenization of pigmentation irregularities with repeat treatments (Fig. 3).

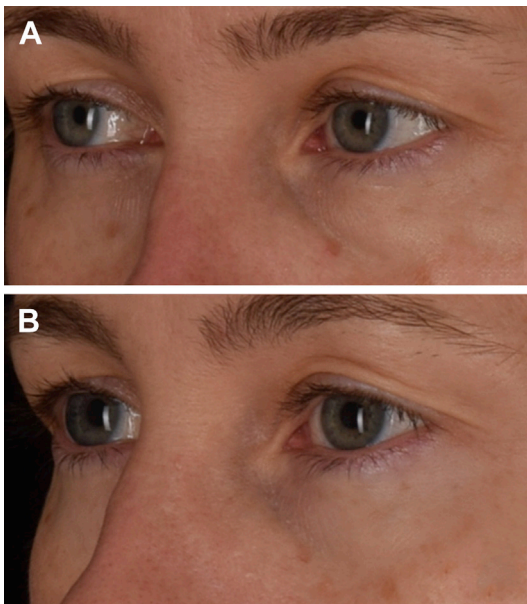


Fig. 3. A 45-year-old female patient (A) before and (B) after 3 treatments of infraorbital PRF injections spaced 4 to 6 weeks apart to correct pigmentation irregularities, stimulate volume restoration, improve fine lines, and reduce under-eye hollowing.

The author has also treated patients with a combination of PRF and hyaluronic acid filler (Fig. 4, Video 1). Together, PRF and filler synergistically improve moisture retention and create a scaffold for collagen growth as the body metabolizes the filler over time. The author has anecdotally found that a concentration of 2 parts filler to 1 part PRF will lead to a sustained filler effect and still harness the advantages of the PRF.

Fat Grafting

Autologous fat transfer, although slightly more invasive than office-based hyaluronic acid fillers, efficaciously restores volume loss. Unlike conventional dermal fillers, fat grafts provide potentially permanent volume restoration; however, only roughly half of the transferred cells survive.⁴⁶ Fortunately, PRF shows promise in improving fat retention (Fig. 5).

Adipose tissue is considered an exceptional stem cell source.²⁸ Furthermore, subcutaneous fat is an especially attractive source of progenitor cells because of its accessibility, abundance, and the existence of a supportive stromal vascular fraction (SVF).⁴⁷ The SVF of the abdominal subcutaneous tissues is regarded as an exceptional fat harvesting location considering its abundant supply of adipose-derived stem cells.⁴⁷ However, stem cell viability can be difficult to sufficiently sustain while in transit during fat transfer. Liu and colleagues⁴⁸ highlighted the enhancement of fat transfer with PRF supplementation, detailing that implementing PRF reduced resorption and improved retention of fat grafts. PRF's effect on fat survival likely results from its prolonged growth



Fig. 4. (A) Before and (B) immediately after treatment of a 40-year-old female patient with hyaluronic acid filler and PRF injected to infraorbital hollows.



Fig. 5. (A) Before and (B) 3 months after fat transfer supplemented with PRF, an endoscopic brow lift, and a face lift were performed on this 66-year-old female patient.

factor release and the ability of the autologous fibrin matrix to sufficiently support stem cell transfer. A study by Keyhan and colleagues⁴⁹ supported this premise, reporting that PRF more effectively improved fat graft retention than PRP. [Video 2](#) depicts the process conducted to supplement fat transfer with PRF.

Facial Surgery

As invasive treatments, facial surgeries elicit strong clotting and wound-healing responses.

The resulting blood clots consist mainly of erythrocytes.¹ Applying PRF to the surgical site effectively replaces the abundance of erythrocytes with fibrin, leukocytes, stem cells, and platelet-derived growth factors. This results in accelerated wound healing and attraction of MSCs to the site, laying the foundation for tissue regeneration, collagen remodeling, and a sustained cosmetic result.

In rhinoplasties, cartilage grafts are frequently needed to achieve optimal results. Cartilage grafts are formed from diced autologous or cadaver

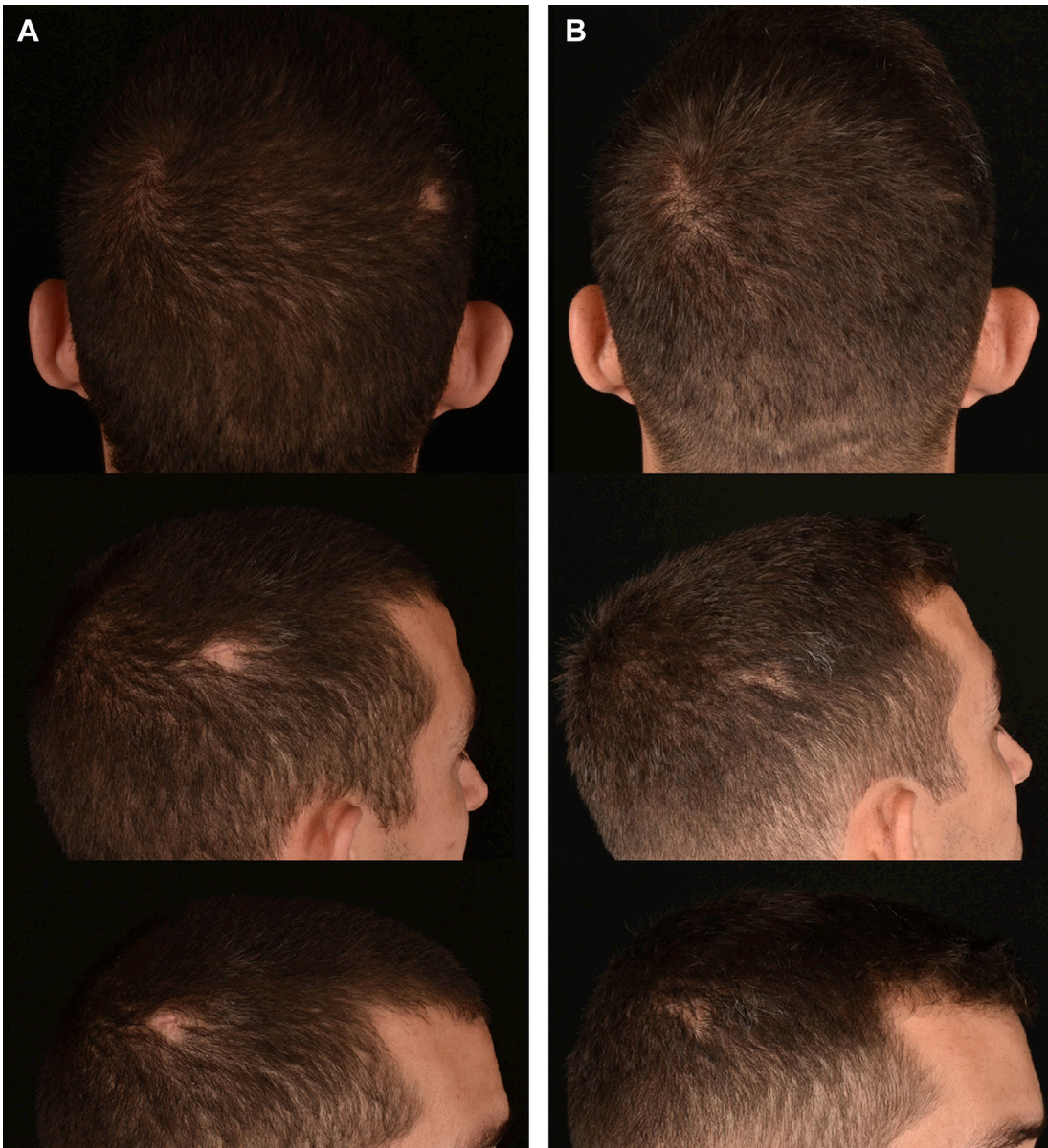


Fig. 6. (A) Before and (B) after 1 session of PRF injections to treat the appearance and hair growth of a lateral parietal trauma-induced scar of a 28-year-old male patient. Progress photos were obtained 6 months after treatment. Before treatment, hair growth was dormant for 5 weeks.

cartilage. When used alone, diced cartilage may scatter after placement, resulting in palpable or visible structural irregularities.^{50,51} PRF aids in forming and depositing cartilage grafts by acting as a physiologic glue that enhances the consistency and pliability of the grafts and reduces the probability of graft rejection owing to its autologous nature (Video 3). Studied in a rabbit model, PRF effectively improved cartilage graft viability,⁵⁰ and, in another study, it stimulated cartilage regeneration more so than PRP.³⁴

Hair Loss and Scar Therapy

The primary author has found that PRF injections improve scar appearance and stimulate hair growth where hair follicles are present but inactive (Fig. 6).

THE FUTURE OF PLATELET RICH FIBRIN

The widespread applications of PRF solidify its place among autologous blood concentrate therapies as both a primary and supplementary medical tool. Further research is expected to uncover additional benefits to be obtained from PRF's bioavailability, autologous nature, and regenerative properties.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found online at <https://doi.org/10.1016/j.fsc.2019.03.005>.

ACKNOWLEDGMENTS

The authors thank Marissa Kudo for her additions in assembly of information for this article, and Fred Wilson for his editorial contributions.

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