Platelet-Rich Plasma: Principles and Applications in Plastic Surgery

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Abstract

Platelet-rich plasma (PRP) is an autogenously harvested liquid platelet concentrate extracted from a patient's peripheral blood that contains higher than baseline concentrations of growth factors and cytokines. This innovative new technology has demonstrated great promise in the field of plastic surgery, and its use has been evaluated in several clinical settings including wound healing, hair restoration, and skin rejuvenation. The goal of this article is to explain the biology behind PRP and to review the basic principles involved in its preparation. This will be followed by a discussion of some clinical applications of PRP in both aesthetic and reconstructive plastic surgery.

Keywords

- platelet-rich plasma
- PRP
- growth factors
- wound healing
- skin rejuvenation
- bone healing
- hair growth

Following tissue injury, the healing process of both soft and hard tissues is mediated by a series of complex interactions, both inside and outside the cell, that are regulated by biologically active proteins.[1–3] While some aspects of this process remain incompletely understood, advances over the last few decades have demonstrated that platelets play a prominent role in wound healing.[3,4] The fact that platelets secrete growth factors and active metabolites critical to the process of wound healing suggests that their application could positively influence clinical situations requiring rapid healing and tissue regeneration.

Platelet-rich plasma (PRP) is a preparation of autologous plasma enriched with a platelet concentration above normal levels. PRP therapy has gained popularity in regenerative medicine with clinical reports and applications in a multitude of specialties, including plastic surgery. With the vast majority of these studies yielding excellent outcomes, there is strong evidence to support the clinical use of PRP. However, most of these studies are limited by their retrospective design, lack of demonstrable objective evidence, and failure to describe the baseline characteristics and activation process of PRP.[5,6] The goals of this article are to describe the basic biologic principles of platelets' role in wound healing and to discuss clinical applications of PRP in plastic surgery.

Platelet Biology and Wound Healing

Platelets are derived from megakaryocytes, which are myeloid cells found primarily in the bone marrow.[7–9] In preparation for platelet synthesis, megakaryocytes enlarge in size, amplify their DNA, and synthesize the required machinery needed for platelet biogenesis.[8] Terminally differentiated megakaryocytes then reshape their cytoplasm to form pseudopodia that extend into bone marrow sinusoids, forming a dense network of interconnected proplatelets.[7] The multilobed megakaryocyte nucleus is extruded and degraded, and platelets then swell and bulge off of the terminal pseudopodia and are released into the bloodstream.[9]

Successful wound healing can be separated into three phases—inflammation, proliferation, and remodeling.[2,10,11] Platelets play a critical role in all three phases of wound healing.[10,11] Inflammation is characterized by the platelet-mediated establishment of hemostasis and the release of chemotactic growth factors.[10,11] When tissues are damaged, circulating platelets are exposed to subendothelial collagen.[12] This interaction activates platelets, causing them to aggregate and release the contents of their α-granules, including ADP, thromboxane A_2, and calcium ions.[13] These substances cause both vasospasm and further platelet

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aggregation, providing temporary primary hemostasis by facilitating the formation of a platelet plug.[2]

More permanent secondary hemostasis is achieved through activation of the clotting cascade via the intrinsic and extrinsic coagulation pathways.[13] Platelets facilitate various steps in both of these pathways, which ultimately converge and lead to the production of a fibrin mesh that stabilizes the initial platelet plug and forms a more permanent blood clot.[14] Soon after clot formation, platelet-derived actin and myosin myofibrils contract, leading to clot retraction and further aiding in hemostasis.[14]

In addition to containing hemostatic factors, α-granules also hold a variety of growth factors, chemokines, and cytokines (►**Table 1**).[4] The fibrin matrix formed by the coagulation pathways acts as a scaffold for these substances, maintaining their proximity to the site of endothelial injury and acting as a guide for subsequent cell migration, proliferation, differentiation, and extracellular matrix (ECM) synthesis.[10,11,15] The first cells recruited by these signaling molecules are neutrophils, which protect the injured region from infection and remove tissue debris for hours to days following tissue injury.[12] Monocytes then recruited and differentiate into macrophages, the predominant cell type in the days to months following injury.[12] Next, mesenchymal stem cells and fibroblasts migrate into the damaged region in preparation for the proliferation stage of wound healing.[10] This inflammatory response is normally established within the first 24 hours and can extend for up to 2 to 6 days after tissue injury.[16]

Proliferation is characterized by additional removal of damaged and necrotic tissues and replacement via ECM elaboration.[10,11] The mesenchymal stem cells that were recruited by cytokines during the inflammatory phase differentiate into fibroblasts, osteoblasts, chondrocytes, and other cell types specific to the local tissue environment.[10] Fibroblasts begin to elaborate ECM, providing an environment for nearby endothelial cells to proliferate and initiate the process of angiogenesis.[2,10] Together, these migrating cells and their platelet-coordinated actions bring the proliferation phase to a close with the formation of granulation tissue—the transient, soft, pink, well-vascularized tissue that serves as the foundation for tissue repair.[11,17] These processes begin within the first 48 hours and can continue for up to 14 to 30 days after tissue injury.[16]

The final phase of wound healing, remodeling, is characterized by reorganization of newly generated tissues to resemble the original tissue as closely as possible.[2,10] Early in the remodeling phase, fibroblasts differentiate into myofibroblasts, causing the wound to contract and re-epithelialize.[12] The complete process of remodeling, however, can take years to occur.[2,10] Over time, excess ECM is removed and collagen fibers are oriented along tension lines to provide maximal wound bed strength.[2,10] The ultimate goal of remodeling is to restore integrity to the damaged tissue—not necessarily to restore its full original form or function.[10] In soft tissues and skin, remodeling is characterized by replacement of the original tissue with a scar that fills out the damaged space.[6] In bone, however, scar does not form, and the remodeled bone is indistinguishable from its appearance prior to being damaged.[10] Ultimately, fully healed tissues may regain up to 80% of their original strength compared with unwounded tissue.[18]

From initial tissue damage to tissue remodeling and scar formation, platelets play an integral role in every step of wound healing. One translational application of this knowledge has been the development of PRP—an autogenous, platelet-enriched medium with the ability to augment wound healing and enhance tissue regeneration. ►**Fig. 1** is a schematic representation of the role of platelets in wound healing.

Table 1 Key growth factors stored in platelet α-granules and their functions

Growth factor	Function
EGF	Cell proliferation, granulation tissue, re-epithelialization, tensile strength
FGF	Cell proliferation, stem cell differentiation, angiogenesis, collagen production
PDGF	Cell proliferation, chemotaxis, angiogenesis
TGF-β	Angiogenesis, collagen production, re-epithelialization, protease synthesis
VEGF	Angiogenesis

Abbreviations: EGF, epidermal growth factor; FGF, fibroblast growth factor, PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β; VEGF, vascular endothelial growth factor.

Platelet-Rich Plasma Principles

As previously defined, PRP is a fraction of autologous blood plasma containing highly concentrated levels of platelets. Other terms have been used to describe platelet preparations in the literature, including platelet concentrate, platelet releasate, and platelet gel. A wide variety of PRP synthesis protocols exists, all of which involve the basic steps of PRP preparation as follows: (1) blood collection, (2) centrifugation, (3) plasma aspiration, (4) potential second centrifugation, (5) selected supernatant removal, (6) mixing/resuspension of platelets, (7) activation, and finally (8) application. All protocols involve blood collection immediately before use and one or more differential centrifugation steps. The goal of differential centrifugation is to separate the patient's whole blood based on density into three layers: plasma, red blood cells (RBCs), and a buffy coat layer rich in platelets and leukocytes. It is important to realize that several factors during the preparation process can affect the final PRP product, such as temperature, force and time of centrifugation, sequence and number of centrifugations, use of anticoagulation, and mechanism of activation. For example, longer and more forceful centrifugation has been reported to push platelets further down in the sediment layer and potentially affect growth factor concentration and cellular integrity.[19] After the RBC layer is discarded, additional centrifugation can produce several different platelet preparations.

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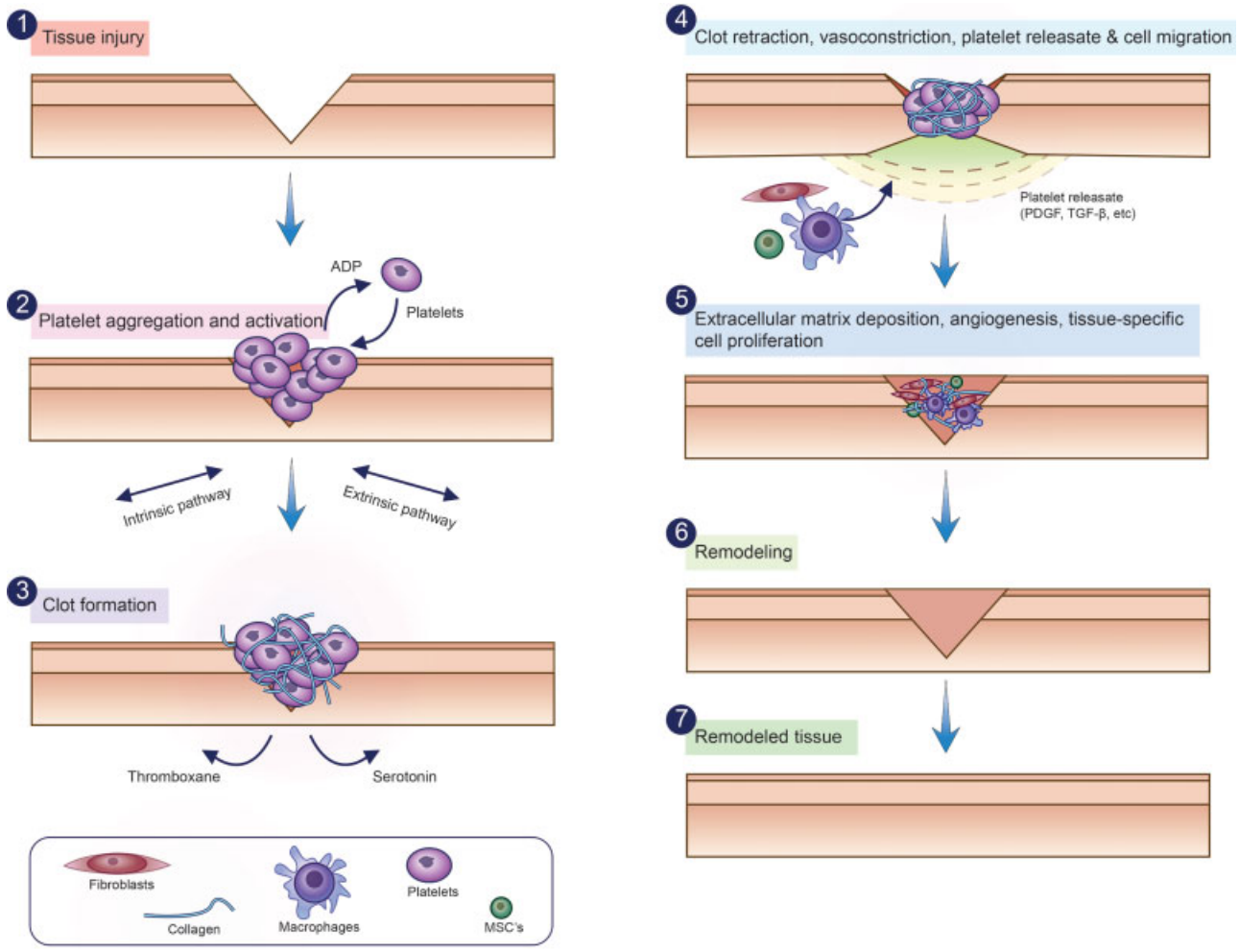

Fig. 1 Schematic representation of the role of platelets in wound healing. MSCs, mesenchymal stem cells; PDGF, platelet-derived growth factor; TGF-β, transforming growth factor β.

Types of PRP and Platelet Concentration

Based on the extent of buffy coat inclusion and the use of anticoagulation, four PRP preparations have been classified: (1) pure PRP (P-PRP), (2) leukocyte-rich PRP (L-PRP), (3) pure platelet-rich fibrin (P-PRF), and (4) leukocyte-rich platelet-rich fibrin (L-PRF).[20] PRP is the most common commercially available preparation. The pure form of PRP was the first platelet preparation to be created and utilized; however, due to its highly demanding processing technique, leukocyte rich forms were soon introduced.[21] The types of platelet preparations are summarized in ►**Table 2**.

While P-PRP and L-PRP preparations are both in a liquid platelet suspension and involve an activation step to release growth factors, PRF is an activated fibrin-based biomaterial/gel. PRF also differs from PRP by having a larger volume and lower platelet concentration. The most common commercially available form of PRF is P-PRF; a leukocyte-rich form also exists but is not widely used in plastic surgery. When preparing P-PRF, the blood is first centrifuged at a low speed with no anticoagulants to separate the blood into its three layers. The plasma layer (which contains the fibrinogen) and the buffy coat layer are then removed and used together. Activation with calcium, thrombin, or direct tissue contact leads to both the conversion of fibrinogen to polymerized fibrin as well as platelet degranulation and release of growth factors. The fibrin network formed provides an environment

Table 2 Types of platelet preparations

	Leukocyte poor	Leukocyte rich
PRP	P-PRP (small volume, minimal fibrin polymerization)	L-PRP (small volume, minimal fibrin polymerization)
PRF	P-PRF (larger volume, dense fibrin polymerization)	L-PRF (larger volume, dense fibrin polymerization)

Abbreviations: PRP, platelet-rich plasma; PRF, platelet-rich fibrin; L-PRF, leukocyte-rich PRF; L-PRP, leukocyte-rich PRP; P-PRF, leukocyte-poor PRF; P-PRP, leukocyte-poor PRP.

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for growth factor binding, cellular migration, and collagen deposition.[15,22]

Reports on the role of PRP leukocytes have been inconsistent and controversial.[23] Anti-infectious properties and elevated VEGF content have been reported as some of the beneficial effects observed when leukocytes are included in PRP preparations.[24,25] However, other studies report an association with increased inflammation and tissue damage.[24,25] In addition, contained neutrophils may inhibit the wound healing process by releasing massive reactive oxygen species (ROS).[3] Unfortunately, details of the leukocyte content is often undocumented by studies, making it difficult to draw any outcome comparisons.[26]

It is also important to mention that in clinical practice, determining precisely the exact content of a platelet preparation is not as simple. It is therefore not surprising that accurate terminology is frequently avoided in many publications, and the broad term of PRP is used instead.[26]

Given the broad range of normal platelet concentrations in whole blood, it is crucial to determine and report the baseline concentration of a patient's platelets. Furthermore, a dose response relationship has been previously described between platelet concentration and proliferation of both stem cells and fibroblasts as well as the formation of type I collagen.[27] Therefore, knowing the exact platelet content of PRP is important to establish clinical effectiveness, guide treatment protocols, and avoid adverse events. Otherwise administering PRP becomes a blind process where unknown levels of bioactive molecules are utilized. Reporting of platelet concentrations at baseline and in the final product should be a requisite for future all clinical studies involving PRP.

Anticoagulation and Activation

The choice of anticoagulant can impact both the final platelet concentration as well as the function of a given PRP preparation.[19,28] Many anticoagulants have been described in the literature, including sodium citrate, trisodium citrate, acid citrate dextrose, and heparin.[26,29] While the majority of studies fail to report their anticoagulant, sodium citrate and acid citrate dextrose are among the most reported.[26] Nonetheless, comparing the superiority of one over the other remains difficult due to a host of confounding variables. In addition, inquiring about patient medications should always be done prior to PRP preparation, as platelet function can also be affected by many drugs, such as aspirin and statins.[30]

The step in which anticoagulation is utilized or reversed determines if the final product is considered to be activated at the time of application. The activation process is often performed exogenously by adding calcium-based products, which reverses the anticoagulation and allows coagulation and platelet activation to take place.[26] There is no clear consensus on the benefits and detriments of exogenous activation, yet the majority of studies activate PRP at the time of application.[26] Following activation, 70% of growth factors are released within 10 minutes, and nearly all the remaining growth factors within one hour.[31]

PRP processing protocols are abundant in the literature, all with different final platelet concentrations and with various alterations in anticoagulation, centrifugation, or activation techniques.[19,26,32,33] These studies highlight the fact that establishing a standardized protocol is paramount to more effective future PRP utilization, as small changes in every step of the preparation process can result in significantly different final products and, in turn, influence the clinical efficacy of each PRP preparation.[34]

Clinical Applications

Platelet-rich plasma functions as a delivery medium for a multitude of cytokines and growth factors that contribute to tissue regeneration. Combined with its autologous nature and availability, such properties make PRP a highly attractive treatment modality in many plastic and reconstructive surgical applications.

Wound Healing

In a systematic review by Sommeling et al, 9 studies, including 6 clinical trials, investigated the efficacy of PRP in promoting wound healing.[29] Primary outcomes to assess wound healing included wound healing rate, re-epitheliazation, and wound closure. Significantly favorable outcomes were reported by almost all of the articles reviewed. These beneficial effects were attributed to enhanced neoangiogenesis and granulation tissue formation in wounds treated with PRP and were most likely to occur when PRP was applied repeatedly to the wound bed. Furthermore, shorter time to healing and to reconstructive surgery, lower amputation rate, lower rates of edema and ecchymosis, and decreased pain were all reported as additional advantages with the use of PRP. Such advantages can result in the reduction, and possible elimination, of the need for postoperative drains and analgesic medications. None of the studies reported any PRP-related side effects.

This study also reported on a wide variety of chronic wounds and ulcers that were treated with PRP, particularly those in the lower limbs, including both diabetic and nondiabetic ulcers. Differences in the PRP preparation protocols as well as the method and number of applications were also noted.[29] Due to such differences between these protocols, the authors found it challenging to make accurate comparisons between different PRP preparations and traditional therapy.

Fat grafting

Fat grafting has gained tremendous attention in recent years, particularly in facial plastic surgery, due to its ability to restore contour and treat atrophic lesions. Platelet preparations have been combined with autologous fat transfers to improve volume maintenance and reduce facial scarring. As resorption has historically plagued fat grafting attempts, the addition of PRP has been hypothesized to increase graft longevity, thus resulting in superior results. Wound healing, nutrient support, angiogenesis, and adipose-derived stem cell proliferation (ADSCs) are all enhanced when PRP is combined with fat grafting.[35] These findings are further supported by in vitro studies showing that, when activated,

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PRP contains significant amounts of platelet-derived growth factor (PDGF) and transforming growth factor-β 1 (TGF-β1) that can substantially promote the proliferation of ADSCs and dermal fibroblasts.[36]

Case control studies comparing the outcomes of PRP-enhanced fat grafting to conventional fat grafting demonstrated a statistically significant decreased time to re-epithelialization.[29] In the setting of facial scarring, fat grafting combined with activated PRP resulted in superior contour restoration and volume maintenance after one year of surgery when compared with fat grafting alone.[37,38] Notably, though, volume maintenance was evaluated differently among studies; utilized methods included magnetic resonance imaging, ultrasonography, and three-dimensional computed tomography.[29,37,38]

However, when PRP was combined with breast fat grafting, no beneficial effects were demonstrated when compared with the conventional approach.[39] In fact, the use of PRP in the setting of breast fat grafting resulted in higher rates of fat necrosis and no reduction in the total number of fat grafting sessions.[39]

Despite this notable exception in the realm of breast fat grafting, studies describing the combined use of platelet preparations and fat grafting suggest overall benefits of improved fat survival and wound healing.

Bone Grafting

In the field of plastic and reconstructive surgery, bone grafts can be used in several settings, such as cleft palate surgery and mandibular reconstruction. The first to explore the regenerative potential of PRP to enhance the success of bone grafting were Marx et al in the year 1998.[40] In this study, when compared with controls, PRP-enriched bone grafts showed faster radiographic maturation rate as well as higher bone density.[40] Since this initial study, numerous others have investigated the effects of PRP on the survival of bone grafts, including several randomized controlled trials.[29,41,42] Collectively, these studies have shown that PRP-enriched bone grafts have higher bone augmentation, shorter time to bone regeneration, decreased postoperative pain, lower rates of hematoma and edema, and overall superior outcomes.[29,41,42]

Aesthetic Applications

Skin and Face Rejuvenation

Given their wound healing and tissue regeneration properties, it is no surprise that plastic surgeons have used platelet preparations as adjuncts in many skin rejuvenation procedures. Both topical applications and skin injections have well-documented benefits in the literature when used in patients with facial wrinkles, acne scars, or photo-damaged skin.[43] Most published literature consists of case reports or case series studies, and very few randomized controlled trials. Across all study types, there is often no mention of the process or specific type of the platelet preparation utilized. In addition, the lack of universal clinical outcome measures makes valid comparisons nearly impossible.

Despite these limitations, the combined use of PRP with skin rejuvenation procedures such as microneedling or fractional laser is becoming increasingly popular and is often referred to as the "vampire facial." While it often refers to the combination of PRP with microneedling, the term "vampire facial is also used to describe the use of PRP after fractionated laser or the direct injection of PRP into the skin. After fractional laser resurfacing or microneedling, small holes are formed in the skin that can act as an effective route for the delivery of PRP. In 2016, Asif et al evaluated the effects of microneedling with subsequent PRP application where each patient with acne scarring received distilled water in one hemiface and PRP in the other hemiface.[44] Using Goodman's Quantitative scale, the PRP-treated side showed a greater reduction in atrophic acne scarring compared with when microneedling was used alone. Further studies using the same principle investigated the effect of PRP following fractionated laser resurfacing and demonstrated improved overall appearance and decreased erythema and edema on the PRP-treated side.[45] Other reported advantages of PRP include improved patient satisfaction, enhanced skin elasticity, thicker neocollagen growth, and less inflammatory pigmentation.[43]

Facelift and Rhytidectomy

While most applications of PRP in aesthetic surgery have shown improved results, those related to the use of PRP with facelifts were not as promising. In an analysis of 1,089 facelifts in which 587 patients received PRP and the remaining patients underwent the superwet technique, no difference was found in hematoma rates between the two groups.[46] Similar results were demonstrated by another study in which the authors followed a split-face study design where PRP was applied unilaterally and then compared with the other side.[47] Nineteen observations regarding the PRP side were reported; 15 were positive, 3 were indifferent, and 1 was negative.[47] The authors concluded that PRP may reduce edema and ecchymosis following facelift; however, no statistically significant differences between the two sides were noted.[47]

Hair Restoration

The use of PRP for hair loss has demonstrated great potential in promoting hair regrowth and has been investigated by numerous studies in both male- and female-pattern baldness.[26,43] In comparison to other PRP applications, the outcomes of PRP use in hair restoration are straightforward and quantifiable, making it possible to compare outcomes objectively.

Several methods of applying PRP onto the scalp have been described in the literature with no consistent single method for optimal PRP concentration dosing.[48,49] PRP has been applied using subcutaneous or intradermal injections to all areas of the scalp suffering from alopecia. Variable dosage frequencies, durations of treatment, and surface areas have been reported. Injection volume typically ranges from 0.8 to 12 cm^3.[48] While most of the literature describes the use of PRP on areas of alopecia, some studies have investigated the

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effect of PRP as an adjuvant to hair transplantation and follicular unit extraction (FUE) procedures.[48,50]

In 2017, Sand et al conducted a systematic review of 17 studies exploring the effect of PRP on hair restoration.[43] While the majority of these studies demonstrated positive effects, two articles described no significant improvement. Such conflicting results can be traced back to the heterogeneity of the utilized protocols. Nevertheless, collectively these studies point to the effectiveness of PRP in hair restoration as well as the need for multiple injections to achieve significant results.[45]

When compared with placebo, patients treated with PRP showed significantly increased hair growth, increased K_i-67 levels (marker for cellular proliferation), and decreased hair dystrophy.[51] PRP's mechanism of action in patients with alopecia involves promoting stem cell differentiation, activating antiapoptotic pathways to prolong survival of dermal papilla cells, prolonging the anagen phase, and stimulating proangiogenic pathways, thus increasing the perifollicular vascular plexus.[52]

Limitations

The main limitation when evaluating the clinical applications of PRP is the variation in established preparation protocols. Multiple commercial systems are available that utilize different centrifugation protocols and therefore result in variable platelet and growth factor concentrations. Furthermore, the presence or absence of leukocytes, anticoagulants, and activating factors can further influence the quality of PRP and the final clinical outcome. The lack of a standardized treatment regimen for most of its applications, the need for multiple injections, and the limited amount of long-term data are also some of the current important limitations to PRP therapy.

Nevertheless, the future of PRP within the field of plastic and reconstructive surgery is very promising. Moving forward, clearly defined PRP preparation protocols and application guidelines will be required to achieve the best outcomes and validate the potentially high efficacy of PRP.

Conclusion

Platelet-rich plasma is an increasingly popular technology that has demonstrated many promising outcomes in the field of plastic and reconstructive surgery. Numerous innovative PRP applications are currently being evaluated, with skin rejuvenation and hair restoration having the highest level of evidence. To date, no major side effects have been reported related to the use of PRP, making it a safe, inexpensive, and readily available treatment modality for a variety of aesthetic purposes. High-quality randomized controlled trials with objective outcomes and standardized protocols are necessary to better evaluate the effects of PRP. Should these steps be taken, scientifically validated recommendations and indications to guide future PRP applications can be established.

Conflicts of Interest
None declared.

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