International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Platelet-Rich Plasma in the Management of Atrophic Acne Scars: Mechanisms, Clinical Applications, and Safety

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Abstract:

Background: Acne scarring is a complication of inflammatory acne that can cause substantial cosmetic and psychological burden. Atrophic scars, including ice-pick, boxcar, and rolling subtypes, result primarily from inadequate collagen deposition and disorganized extracellular matrix remodeling. Platelet-rich plasma (PRP) has emerged as an autologous regenerative treatment that delivers concentrated platelets, growth factors, cytokines, and adhesive proteins to damaged dermal tissue. This review summarizes the biological composition, preparation, mechanisms, clinical applications, safety, and limitations of PRP in managing atrophic acne scars. Platelet-derived growth factor, transforming growth factor-beta, vascular endothelial growth factor, epidermal growth factor, insulin-like growth factor-1, and fibroblast growth factor-2 promote fibroblast activity, angiogenesis, re-epithelialization, collagen synthesis, and matrix organization. Treatment outcomes depend on platelet concentration, centrifugation protocol, anticoagulant selection, activation method, and route of administration. Available evidence indicates that intradermal PRP can improve scar severity, dermal thickness, and skin texture, although responses vary among patients and protocols. Greater clinical benefits are frequently reported when PRP is combined with microneedling, subcision, or fractional carbon dioxide laser therapy, because these procedures provide complementary mechanical or thermal stimulation. PRP may also reduce post-procedural erythema, edema, inflammation, and recovery time. Adverse effects are generally mild and transient because the product is autologous; however, strict aseptic preparation and appropriate patient selection remain essential. Platelet-rich fibrin may provide more sustained growth-factor release, but additional comparative trials are required. Overall, PRP is a promising, safe adjunct for atrophic acne scars, while standardized preparation methods and high-quality controlled studies are needed to define optimal protocols and long-term effectiveness.

Keywords: Platelet-rich plasma; atrophic acne scars; scar remodeling; microneedling; subcision; fractional CO2 laser; platelet-rich fibrin.

Introduction:

Acne is a common condition that affects up to 80 percent of the adolescent population. It is caused and characterized by multiple factors including *Cutibacterium acnes* activity, increased sebum production, androgenic stimulation, follicular hypercornification, lymphocyte, macrophage, and cytokine activation. Inflammatory acne can result in permanent scars, relating to both its severity and delayed treatment. Acne scars can be classified into two different types: atrophic, and hypertrophic, with the atrophic scars being the most common type **(1).**

Atrophic acne scars are sunken or pitted marks on the skin, formed from a loss of tissue when the skin doesn't produce enough collagen to repair deep acne damage, leading to indentations like ice-pick, boxcar, or rolling scars. Prevention with early acne treatment is best, but professional treatments like microneedling, lasers, chemical peels, and subcision can stimulate collagen and improve their appearance by resurfacing the skin **(2, 3).**

In recent decades, the paradigm of treatment of acne scars has shifted from purely destructive or ablative methods toward regenerative medicine, with platelet-rich plasma (PRP) emerging as a pivotal autologous therapy. By delivering a concentrated milieu of growth factors, cytokines, and bioactive proteins, PRP facilitates the restoration of dermal architecture and promotes the reorganization of ECM **(4)**.

- **Biological Composition of Platelet-Rich Plasma:**

Platelet-rich plasma is an autologous blood-derived product characterized by a platelet concentration significantly higher than the physiological baseline, typically achieved through differential centrifugation of peripheral blood. The therapeutic premise of PRP lies in the α-granules of platelets, which house a dense reservoir of over 1,100 proteins and bioactive factors that orchestrate the regenerative response **(5)**.

Upon activation, platelets undergo degranulation, releasing growth factors (GFs) that bind to transmembrane receptors on target cells such as fibroblasts, endothelial cells, and mesenchymal stem cells, **table 1**. This binding triggers intracellular signaling pathways that promote cell recruitment, proliferation, and the synthesis of new ECM components **(6, 7).**

Table (1): Biological Roles of Key PRP Components in Dermal Repair **(7)**

Component	Full Name	Physiological Function in Scar Remodeling
PDGF	Platelet-Derived Growth Factor	Mitogenesis of fibroblasts promotes collagen and matrix synthesis
TGF-β	Transforming Growth Factor-Beta	Regulates ECM homeostasis; promotes collagen and elastic fiber formation
VEGF	Vascular Endothelial Growth Factor	Primary mediator of angiogenesis; enhances microcirculation and nutrient delivery
EGF	Epidermal Growth Factor	Stimulates keratinocyte migration and re-epithelialization
IGF-1	Insulin-like Growth Factor-1	Promotes cell differentiation and works synergistically with other GFs
FGF-2	Fibroblast Growth Factor-2	Enhances tissue remodeling and supports angiogenesis

PDGF, Platelet-Derived Growth Factor, TGF-B, Transforming Growth Factor-Beta, VEGF, Vascular Endothelial Growth Factor EGF, Epidermal Growth Factor, IGF-1, Insulin-like Growth Factor-1, FGF-2, Fibroblast Growth Factor-2.

In addition to these growth factors, PRP contains vital plasma proteins like fibrin, fibronectin, and vitronectin, which provide a provisional scaffold for cell adhesion and migration. The presence of leukocytes in certain PRP formulations, specifically Leukocyte-rich PRP (L-PRP), introduces an immunomodulatory dimension, facilitating the transition of macrophages from a pro-inflammatory (M1) to a pro-regenerative (M2) phenotype, thereby optimizing the healing microenvironment **(8)**.

- **Standardization of PRP Preparation:**

The clinical efficacy of PRP is highly dependent on the preparation protocol, as variations in centrifugation parameters, anticoagulants, and activation methods directly influence the final platelet yield and growth factor concentration. A lack of standardization has historically contributed to variable results across clinical studies **(8)**.

Platelet rich plasma is typically prepared using differential centrifugation, which separates blood components based on their specific gravity. The process relies on relative centrifugal force (RCF), measured in units of gravity (g), calculated using the formula $g = (1.118 \times 10^{-5}) \times R \times S^2$, where R is the rotor radius in centimeters and S is the speed in revolutions per minute (rpm) **(9)**.

The "double-spin" manual method is widely regarded as the gold standard for dermatological needs due to its superior platelet yield compared to single-spin systems. In the first "soft spin," red blood cells (RBCs) are sedimented at the bottom, while the plasma and platelets remain in the supernatant. The second "hard spin" precipitates the platelets to form a pellet, which is then resuspended in a small volume of plasma to create the final PRP **(10)**.

Temperature also plays a critical role; while room temperature (20°C – 24°C) is standard, some evidence suggests that lower temperatures (12°C – 16°c) may better preserve platelet viability during the concentration process. To prevent premature activation, Acid Citrate Dextrose A (ACD-A) is the preferred anticoagulant, as it maintains the metabolic integrity of the platelets better than ethylenediaminetetraacetic acid (EDTA) or heparin **(10)**.

Activation and Release Kinetics:

Prior to application, PRP is often activated to ensure the immediate release of growth factors. Although endogenous activation occurs when PRP contacts dermal collagen, many clinicians use exogenous activators like 10% calcium gluconate or calcium chloride ($CaCl_2$). Research indicates that activation with 10% calcium gluconate enhances the cumulative release of vascular endothelial growth factors and improves the stability of the resulting fibrin gel while others suggest that it is an unnecessary step **(11)**.

Molecular Mechanisms of scar remodeling:

The biological correction of atrophic scars requires the stimulation of dormant dermal fibroblasts to re-initiate the synthesis of structural proteins. PRP achieves this through direct growth factor signaling and through sophisticated mechanobiological interactions **(12)**.

Recent molecular insights suggest that PRP modulates scar progression by targeting the Piezo1channel. The Piezo1 channel is a mechanosensitive ion channel that detects changes in the physical properties of the extracellular environment, such as the stiffness of the dermal matrix. In the context of PRP therapy, growth factors like TGF-β1 activate Piezo1, initiating Ca^{2+} influx and activating calmodulin-dependent kinase II. This pathway enhances the phosphorylation of TGF-β receptor I, creating a positive feedback loop that amplifies TGF-β signaling and drives organized collagen deposition which is fundamental to fill atrophic scars **(13)**.

Platelet rich plasma also addresses the relative hypovascularity often seen in mature scar tissue. By releasing concentrated VEGF and FGF-2, PRP stimulates the formation of new capillary networks (angiogenesis), which improves nutrient delivery and waste removal in the healing dermis. Furthermore, PRP promotes the balance between matrix synthesis and degradation by modulating the expression of MMPs and TIMPs. Specifically, the presence of PDGF and TGF-β encourages the deposition of Type I and Type III collagen while stimulating the formation of new elastic fibers, restoring skin elasticity and thickness **(5)**.

Clinical Efficacy of PRP as Monotherapy:

Clinical trials utilizing the Goodman and Baron global qualitative grading system have demonstrated significant scar improvement following PRP monotherapy. The trials typically involve intradermal injections of PRP into each scar, often spaced 3 to 4 weeks apart. In split-face studies, the mean Goodman and Baron score on the PRP-treated sides demonstrates significantly higher improvement than that observed on control sides **(8, 14)**.

A critical consideration in the delivery of PRP is the route of administration. While both topical and intradermal applications are used, intradermal injection is generally considered more effective, as it delivers the concentrated growth factors directly into the target dermal layer. However, topical application—after microneedling—is better tolerated by patients and associated with less pain **(15)**.

Clinical efficacy of PRP in Multi-Modality Protocols:

In dermatological practice, PRP is most frequently utilized as a synergistic adjunct to physical resurfacing or mechanical release techniques. By combining biological stimulation with mechanical or thermal injury, clinicians can achieve superior outcomes compared to PRP monotherapy **(16)**.

1- Combined PRP and Microneedling (Collagen Induction Therapy):

When PRP is combined with microneedling, the micro-channels created by the needles act as pathways for the PRP to penetrate deeper into the dermis. Evidence from multiple meta-analyses indicates that the addition of PRP to microneedling leads to a statistically significant reduction in scar severity compared to microneedling alone. Clinical studies have shown that patients treated with the combination therapy exhibit thicker, denser skin and a more noticeable reduction in scar volume than those receiving microneedling with saline or other adjuncts **(17)**.

2- Combined PRP and Subcision:

Subcision is the gold-standard treatment for rolling scars, as it manually severs the fibrous bands that tether the scar to the subcutaneous tissue. However, subcision is often limited by "re-tethering," where the released scar attaches back to the underlying tissue during the healing process. Injecting PRP immediately after subcision creates a "spacer" effect, where the volume of the PRP physically separates the released dermis from the underlying tissue, preventing the re-formation of fibrous bands.

This dual action-mechanical release followed by biological stimulation-results in significantly better outcomes for rolling and boxcar scars and poor outcome with icepick scars **(18)**.

3- Combined PRP and Fractional CO2 Lasers:

Fractional ablative lasers work by creating microscopic zones of thermal damage that stimulate intense collagen remodeling. While highly effective, these lasers are associated with significant downtime, including prolonged erythema, edema, and crusting. The application of PRP immediately following fractional laser treatment has been proven to significantly reduce this downtime. The growth factors in PRP accelerate re-epithelialization and reduce the duration of post-laser inflammation. Furthermore, the synergistic effect of the thermal laser injury and the biological PRP stimulation leads to greater improvements in scar depth and overall skin texture compared to laser therapy alone **(16)**.

- **Evolution in plasma preparations: Platelet-Rich Fibrin (PRF):**

As regenerative medicine continues to evolve, platelet-rich fibrin (PRF) has emerged as a second-generation autologous concentrate designed to overcome some of the limitations of traditional PRP. Unlike PRP, PRF is produced through a slower centrifugation process without the addition of anticoagulants or external activators. Comparative trials have shown that PRF is significantly more effective than PRP in treating post-acne scars. The three-dimensional fibrin matrix in PRF acts as a sustained-release delivery system, allowing growth factors to be released gradually over an extended period, which supports more durable tissue regeneration **(19)**.

- **Safety Profile, adverse effects and contraindications:**

Platelet rich plasma is characterized by an exceptional safety profile, as the use of autologous blood eliminates the risk of hypersensitivity reactions, foreign-body reactions, or the transmission of infectious diseases. However, procedural safety depends on the use of sterile techniques during both preparation and application **(20)**.

Adverse effects associated with PRP are typically mild and transient e.g. post-procedural erythema, edema, and mild pain or sensitivity at the injection site. These symptoms typically resolve within 2 to 7 days. While rare, more significant complications such as secondary bacterial infection or post-inflammatory hyperpigmentation (PIH) can occur, particularly if proper aftercare or sun protection guidelines are not followed **(14)**.

- **Contraindication to PRP therapy**: **(21)**

Despite its broad safety, PRP therapy is contraindicated in certain patient populations. Selection criteria are primarily focused on maintaining platelet integrity and ensuring patient safety during the blood-draw procedure.

- **Absolute Contraindications:**
  - Platelet counts < 100,000 mu L (Critical thrombocytopenia).
  - Hereditary or acquired coagulation disorders (e.g., Hemophilia).
  - Sepsis or acute systemic infection.

- Active malignancy, especially near the treatment site.

- **Relative Contraindications:**
  - NSAID use within 48 hours of the procedure (impairs platelet function).
  - Systemic glucocorticoid use within 2 weeks.
  - Anemia with hemoglobin level < 10 g/dL.
  - Chronic liver disease (affects GF synthesis and coagulation).
  - Uncontrolled diabetes or active autoimmune flares.

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