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Review Article

Photoactivated platelet-rich plasma (PA-PRP): A safe and effective treatment for musculoskeletal disorders

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Abstract

Platelet-Rich Plasma (PRP) has emerged as a valuable tool in regenerative medicine due to its high concentration of autologous growth factors and cytokines that promote healing and tissue regeneration. Effective clinical application of PRP necessitates platelet activation, traditionally achieved through agents such as thrombin, calcium chloride, and collagen. However, these methods present limitations including short-lived bioactivity, potential immunogenicity, and regulatory challenges. This review highlights photoactivation a novel, non-chemical activation technique using polychromatic light as a safe, effective, and legally favorable alternative. Photoactivated PRP (PA-PRP) not only triggers sustained growth factor release and ATP synthesis but also enhances platelet activation, tissue repair, and patient outcomes, particularly in musculoskeletal disorders. Supported by recent in vitro and in vivo studies, photoactivation facilitates prolonged bioactivity and cellular responses without adverse effects, positioning PA-PRP as a promising advancement in orthobiologic therapies. Further clinical validation and protocol standardization are warranted to optimize its therapeutic potential.

Keywords: Photo activated PRP (PA-PRP), Platelet-rich plasma, Regenerative medicine, Growth factor release, Musculoskeletal disorders.

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1. Introduction

Recent research indicates that growth factors and cytokines released by platelets in response to injury or pathology play a key role in modulating inflammation and promoting tissue regeneration.[1,2] Platelet-rich plasma (PRP) injections have emerged as a promising treatment in orthobiologics, especially for soft tissue healing, tendon and ligament injuries, bone mineralization, and cartilage regeneration.[1-6]

PRP is an autologous blood product enriched with a high concentration of growth factors, including Vascular Endothelial Growth Factors (VEGF), (Transforming Growth Factor-β TGF-β, Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), and Platelet-Derived Growth Factor (PDGF), Interleukins, Hormones and several hundred other proteins that are released by platelets.[7] These growth factors support local angiogenesis, modulate inflammation, inhibit catabolic pathways, and recruit stem cells and fibroblasts to the site of injury.[7,8] For therapeutic effects, platelets must be activated to release these bioactive molecules.

In the bloodstream, platelets typically remain in a resting, discoid form unless triggered by specific stimuli. Therefore, platelet-rich plasma (PRP) must be activated to prompt the rapid release of growth factors from the platelets. Upon activation, platelets exhibit an initial burst release of growth factors, followed by a sustained release phase; around 70% of the stored growth factors are released within the first hour, and nearly all (close to 100%) are released within 24 hours.[9-10]

2. Materials and Methods

2.1. Platelet activation

In the human body, the platelet activation development is taking placed by tissue damage and the thrombin cascade. However, in clinical applications of PRP, activation is initiated by the addition of products to the sample.

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For clinical applications platelet activation can be achieved by different activators that induce degranulation and release of growth factors from alpha and dense granules.[3] Bovine or autologous thrombin is a traditional activator of platelets but there are concerns regarding its tolerability and adverse effects.

The activation process is one of the main inputs for PRP to work. Common PRP activators include:

1. Bovine thrombin
2. Collagen Type-1
3. Calcium chloride
4. Photo-activation

The optimal concentration of activators remains uncertain. Higher concentrations typically yield rapid but short-lived release of growth factors, whereas lower concentrations offer sustained effects.

2.2. Comparative overview of PRP activation methods

2.2.1. Thrombin

Thrombin is an enzyme that converts fibrinogen into fibrin. Activation with thrombin quickly forms a dense fibrin matrix. The solid formation may inhibit cell migration thus healing. Studies have proven thrombin to be an activator but the release of the growth factors are highest in a short time interval. Thrombin is obtained from bovine sources which could have allergic potential or from autologous sources which equates to increased processing time and larger blood samples.

2.2.2. Calcium chloride

Calcium chloride ($CaCl_2$) is the most common activator used in the majority of clinical studies. Calcium chloride activation has been proven to be less dense than thrombin. A 10% concentration is added to the sample. The amount of growth factors released from an activated sample has been proven to be equal to thrombin activated product. The $CaCl_2$ allows the product to coagulate as apposed to thrombin which causes polymerization. $CaCl_2$ results in a "softer" product initially. However, once activated both thrombin and $CaCl_2$ activated products have limited time for use as both will become dense in a short period of time.

2.2.3. Collagen type 1

Endogenous collagen activates platelets without forming a dense fibrin matrix. Studies have shown, collagen activation provides less growth factors compared to $CaCl_2$ or thrombin activation. Collagen is a weak platelet activator which when tested in the lab resulted in lower growth factor release when compared to thrombin or calcium chloride. The absence of a dense matrix may or may not be advantageous depending on the clinical application.

2.2.4. Photoactivation

Photoactivation is the exposure of PRP to polychromatic light for 10 minutes prior to injection. Most of the effects of photostimulation can be explained by light absorption of cytochrome *C* oxidase (COX) which is the rate-limiting enzyme in terminal phosphorylation in the mitochondrial respiratory chain. The absorption of photons by COX leads to the acceleration of electron transfer reactions and ATP production. The light-induced increase in ATP synthesis and increased proton gradient lead to increased activity of Na^+/H^+ and Ca^{2+}/Na^+ anti-porters, and of all the ATP driven carriers for ions, such as Na^+/K^+ ATPase and Ca^{2+} pumps. Thus, ATP acts to increase intracellular calcium concentration (Ca^{2+}) and calcium mobilization from the intracellular store.

Photoactivation it increases pro-inflammatory cytokine receptors, IL 1 Ra and IL2 RA, beta-endorphin photo modulation with significant benefit in tissue regeneration and healing. With endorphin modulation, PA-PRP has decreased pain and enhanced tissue repair.

According to Dr. Vasilis Paspaliaris, the medical scientist who developed the Adi-Light unit for Adistem Ltd., photoactivation actually does more than that: "Photactivation seems to increase the secretion of tiny vesicles (exosomes) from peripheral blood white blood cells, stem cells and platelets". Adistem were initially made aware of this through its ongoing research into cell photoactivation which has in part been carried out on their behalf by Australia's National Science Agency (CSIRO). PRP is placed in a syringe before injection and PhotoActivated for 10 minutes with Adi-Light 2. (**Figure 1**)

Figure 1: AdiLight-2 device from AdiStem Ltd, Hong Kong. Adistem Ltd. has been supplying photoactivation units since 2008. An improved, lower cost model, Adi-Light 2, has recently been introduced (October, 2012) (More information from www.adistem.com).

A 2020 study in *European Journal of Pharmaceutics and Biopharmaceutics* confirmed that PRP was activated by photoactivation and the controlled release of growth factors were monitored. After photoactivation, ATP secretion then calcium release significantly increased after treatment. Photostimulation triggered Lamellipodia extension, numerous Pilopodia formation and platelet agglomeration as activation indicators. The authors concluded PRP was successfully activated by photoactivation and they found

sustained growth factor release during 28 days proving the activation.

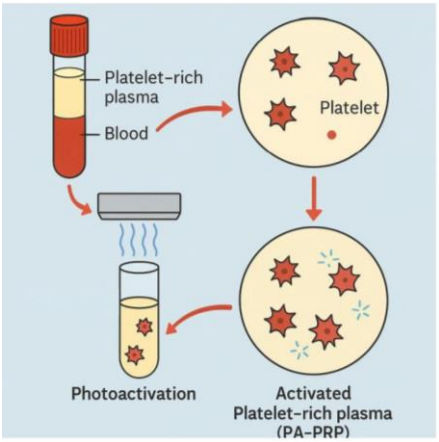

Figure 2: Photo activated Platelet-Rich Plasma (PA-PRP)

Another 2020 study in *Biomedical Materials* demonstrated the use of PA-PRP (**Figure 2**) as a photo-crosslinkable bio-ink for cartilage engineering, emphasizing prolonged growth factor delivery and structural integrity without chemical additives.

Furthermore another study have been demonstrated, the stimulatory effects of PA-PRP promote proliferation and chondrogenic differentiation, which may produce beneficial molecules for the maintenance of auricular cartilage.[12,13] The results of this and other study[2-15] suggest that PA-PRP treatment has a major role to play in the management of OA of the knee.

2.3. Regulatory considerations

2.3.1. Food & drug administration

According to the Indian and USA FDA guidelines, particularly under the National Guidelines for Stem Cell Research, define minimal manipulation and homologous use, autologous PRP is not classified as an HCT/P. However, chemical activators like thrombin or $CaCl_2$ may be considered beyond minimal manipulation. Importantly, photoactivation does not fall under this category, thus avoiding regulatory complications. Photo-Activation appears to be the best method of activation with no side effects or possible future legal ramifications.

2.3.2. Clinical relevance

With over 13,700 studies listed on PubMed, PRP is recognized as a low-risk, high-benefit therapy. However, its clinical success is contingent on effective activation.[9] Among all methods, photoactivation stands out for its safety, simplicity, and legal clarity, making it a highly favorable approach in regenerative medicine.

3. Results

Safety assessments across studies report no adverse reactions or complications. The absence of exogenous chemical activators makes PA-PRP compliant with regulatory guidelines for minimal manipulation.

Clinical evidence including randomized controlled trials shows that PA-PRP significantly improves pain scores, functional outcomes, and joint mobility in knee osteoarthritis and other musculoskeletal conditions. Studies[14] report superior and longer-lasting clinical benefits compared with non-activated PRP. Dermatology studies, such,[5] also demonstrate superior outcomes with PA-PRP.

Pre-clinical studies demonstrate enhanced chondrocyte proliferation, extracellular matrix deposition, and improved stability of PA-PRP-based bio-inks in cartilage tissue engineering, supporting its regenerative potential.

In vitro studies indicate significant increases in ATP production, intracellular calcium release, and platelet cytoskeletal changes such as lamellipodia and filopodia formation following photoactivation. Evidence shows that PA-PRP supports sustained growth factor release for up to 28 days, far longer than thrombin- or $CaCl_2$-activated PRP, which typically release most factors within 24 hours.

Table 1: Comparative summary

S.No.	Parameter	Chemical Activators	Photoactivation (PA-PRP
1	Growth factor release	High but short (24 h)	Sustained up to 28 days
2	Allergy risk	Possible (bovine & thrombin)	None
3	Regulatory concerns	Yes	No
4	Pain reduction	Moderate	Higher and sustained
5	Tissue regeneration	Limited	Stronger (ATP/Ca^{2+} mediated)
6	Regulatory Considerations	May classify as more-than-minimal manipulation	Meets “minimal manipulation” guidelines (India & U.S.)
7	Clinical Efficacy	Effective but variable outcomes	Superior and sustained improvement in OA, cartilage regeneration
8	Ease of Use	Requires chemical agents and preparation	Simple, fast, device-based activation
9	Safety Profile	Dependent on chemical purity; risk of contamination	Excellent; no additives, no immunogenicity

A review of available pre-clinical and clinical studies demonstrates that photoactivated platelet-rich plasma (PA-PRP) provides enhanced biological and therapeutic benefits compared with chemically activated PRP.

4. Discussion

The present review highlights the growing evidence supporting Photo-activated Platelet-Rich Plasma (PA-PRP) as a superior alternative to conventionally activated PRP in musculoskeletal disorders. Traditional chemical activators such as thrombin, calcium chloride, and collagen have been widely used to induce platelet degranulation and growth factor release. While effective, these methods carry limitations including rapid and short-lived bioactivity, risk of immunogenic reactions (particularly with bovine thrombin), and regulatory concerns related to more-than-minimal manipulation.[4] Moreover, thrombin and calcium chloride produce dense fibrin matrices that may restrict cellular migration and limit regenerative potential.

In contrast, photoactivation offers a non-chemical, biologically safe, and regulatory compliant activation method. Studies by Irmak and colleagues demonstrate that polychromatic light activates cytochrome c oxidase, significantly increasing ATP synthesis, intracellular calcium release, and cytoskeletal remodeling, including lamellipodia and filopodia formation hallmarks of platelet activation. This photobiomodulation leads to a stronger and more sustained release of growth factors compared to conventional activation methods. Confirmed that PA-PRP maintains controlled and prolonged growth factor release for up to 28 days, far exceeding the typical 24-hour window seen after chemical activation.

Emerging mechanistic insights suggest that photoactivation may also enhance the secretion of extracellular vesicles, including exosomes, from leukocytes, stem cells, and platelets an effect noted in developmental work by Paspaliaris and colleagues (Adistem). These vesicles play key roles in intercellular signaling and regenerative processes, potentially contributing to the enhanced outcomes observed with PA-PRP.

Clinically, PRP is already supported by robust evidence for effectiveness in treating degenerative cartilage lesions and osteoarthritis.[6,2,14] However, its therapeutic success is closely linked to the activation method used. Given the limitations of chemical activators and the regulatory challenges they pose, photoactivation emerges as the most favorable option.[10] Importantly, photoactivation complies with Indian and U.S. FDA guidelines for minimal manipulation and homologous use, avoiding the complications associated with chemical additives.

In summary, PA-PRP combines enhanced biological activity, superior safety, and a favorable regulatory profile. Its ability to sustain growth factor release, promote cellular regeneration, and reduce adverse effects positions it as a next-generation orthobiologic therapy. Nonetheless, standardized photoactivation protocols and well-designed randomized clinical trials remain essential to validate long-term efficacy and expand its application across diverse clinical indications.[7,8,15]

5. Conclusion

Various types of thrombin or collagen in current use are expensive and have significant side effects. Moreover, exposure of humans to bovine thrombin and collagen can stimulate an allergic response in patients. Calcium sources which are synthetic ingredients have also side effects and toxicity. Besides, all of these chemical agents can activate the PRP only once.

Photoactivated PRP represents a significant advancement in orthobiologic therapies. It provides a non-invasive, biologically compatible activation method that supports sustained healing with reduced adverse effects. As clinical adoption grows, further controlled trials and standardization will be key to validating its efficacy across broader applications.

With favourable safety profiles and no regulatory complications, PA-PRP offers a highly promising and biologically compatible option for clinical application in orthopedic and sports medicine. Its adoption could revolutionize regenerative therapies by overcoming limitations of conventional PRP activation methods. However Further research is needed to fully understand the mechanisms and clinical applications of PA-PRP.

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None.

7. Conflict of Interest

None.

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