Original Article
E Medicine and Public Health. 2024; Vol 02; 13-17
eISSN 3023-3305

Emerging Medicine and Public Health EMPH

The Role of Injectable Platelet-Rich Fibrin in Orthopedics: Where Do We Stand?

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Received: 08 November 2024; **Revised:** 14 December 2024; **Accepted:** 19 December 2024; **Published:** 24 December 2024

Abstract

Injectable Platelet-Rich Fibrin (i-PRF) has emerged as a promising tool in regenerative medicine, particularly in orthopedics, due to its unique biological properties and ease of preparation. i-PRF is an autologous platelet concentrate derived through a simple, anticoagulant-free centrifugation process, resulting in a liquid matrix enriched with fibrin, leukocytes, and growth factors.

These components promote tissue regeneration, angiogenesis, and anti-inflammatory responses, making i-PRF suitable for bone and cartilage repair as well as drug delivery systems. This review discusses the history, biological mechanisms, and clinical applications of i-PRF in orthopedics, highlighting its potential advantages over traditional platelet-rich plasma (PRP). Furthermore, we address the challenges and limitations of i-PRF, including drug stability, release control, and bioactive interactions, underscoring the need for further research to optimize its therapeutic efficacy.

Keywords: ***platelet-rich fibrin; orthopedics; tissue regeneration; anti-inflammatory therapy; regenerative medicine.***

Introduction

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate that was first introduced in the field of oral and maxillofacial surgery by Choukroun and colleagues [1]. PRF was initially used in oral and maxillofacial surgical procedures in 2001 by Choukroun et al., due to its simplicity, cost-effectiveness, and ease of handling [2]. This biological product was conceived as a promising alternative to existing bone grafts and platelet-rich plasma at the time [3].

This autologous biomaterial contains a dense fibrin matrix, along with leukocytes and a wide range of healing proteins [4]. Unlike other platelet preparations, such as PRP, i-PRF is obtained through a single centrifugation process that minimizes blood manipulation and eliminates the use of anticoagulants [4]. Coagulation is an essential step in healing, and the inclusion of anticoagulants during the preparation process of i-PRF hinders the maximization of its regenerative potential [4].

Due to the natural tendency of platelet-rich fibrin to coagulate during centrifugation, centrifugation speeds were reduced to produce a liquid, non-coagulated version of PRF, which later became known as i-PRF or injectable PRF [4]. This liquid form of PRF contained liquid fibrinogen and thrombin that had not yet been converted into fibrin, resulting in improved wound healing due to its clotting ability [5].

In 2015, i-PRF was developed and initially investigated using a very short and slow centrifugation protocol at 700 rpm (60G) for 3-4 minutes with plastic tubes [6]. Since then, various basic research studies have demonstrated the regenerative potential of i-PRF compared to PRP.

Using the technique mentioned above, Miron et al. observed a 2.07-fold increase in platelet concentrations, as well as a 23% increase in leukocytes. Furthermore, it was revealed that horizontal centrifugation of PRF, as opposed to standard fixed-angle devices, resulted in a fourfold increase in cell concentration [7].

Currently, one of the most commonly used protocols involves collecting 10 ml of venous blood in a glass or plastic tube (dry tube) without anticoagulants, and performing centrifugation for 5 to 8 minutes at 60G. This process results in an upper liquid layer of i-PRF that concentrates 2 to 3 times more platelets than whole blood [7-9].

Biological Properties, Anti-Inflammatory Effects, and Mechanisms of Action

i-PRF consists of a fibrin matrix containing a high concentration of platelets, leukocytes, and a variety of growth factors. The growth factors present in i-PRF include platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-β), fibroblast growth factor (FGF), and vascular endothelial growth factor (VEGF) [4]. These growth factors play a crucial role in tissue regeneration by stimulating cell proliferation, differentiation, and migration, as well as promoting angiogenesis [10]. Additionally, the fibrin matrix of i-PRF mimics the natural extracellular matrix and provides a bioactive scaffold for tissue regeneration [4].

Regarding its ability to stimulate angiogenesis, i-PRF demonstrates remarkable potential. Its fibrin matrix activates various mechanisms that promote the formation of new blood vessels, including the release of angiogenic growth factors such as VEGF [11]. This ability to stimulate angiogenesis is crucial for tissue regeneration and healing, as an adequate blood supply is essential to deliver the oxygen and nutrients required for repair processes [12]. The formation of new blood vessels facilitates the delivery of essential elements that support cellular activities, such as the proliferation, migration, and differentiation of cells involved in tissue repair and regeneration [12]. This process of neovascularization

ensures an adequate exchange of metabolites and gases, which is vital for the successful progression of the healing cascade [13].

The anti-inflammatory properties of i-PRF are mediated by its ability to modulate the inflammatory response and promote the resolution of inflammation [14]. Several studies have demonstrated that i-PRF can reduce the expression of pro-inflammatory cytokines, such as interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α), while increasing the expression of anti-inflammatory cytokines, such as interleukin-10 (IL-10) [14-16]. This modulation of the inflammatory response is essential to prevent tissue damage and allow the orderly progression of the healing process.

Another notable biological property of i-PRF is its ability to promote the polarization of macrophages from the pro-inflammatory M1 phenotype to the anti-inflammatory and regenerative M2 phenotype [14]. This phenotypic shift in macrophages plays a crucial role in modulating the inflammatory response and promoting tissue healing and regeneration, as it prevents excessive inflammation that could hinder the healing process [17].

In a study conducted by Nasirzade et al., researchers observed that exposing primary murine macrophages and a human macrophage cell line to saliva and lipopolysaccharides, along with PRF lysates, resulted in a significant reduction in the expression of pro-inflammatory M1 marker genes, such as IL-1β and IL-6 [14]. In parallel, the PRF-conditioned medium increased the expression of tissue resolution markers. These findings led the researchers to conclude that PRF possesses potent anti-inflammatory activity and is capable of altering macrophage polarization from a pro-inflammatory M1 phenotype to an anti-inflammatory and regenerative M2 phenotype.

Antibacterial Properties of i-PRF

i-PRF exhibits antibacterial properties that help prevent infections at the application site. Several studies have demonstrated that i-PRF can inhibit the growth of bacteria commonly associated with infections, such as Escherichia coli, Staphylococcus aureus, and Pseudomonas aeruginosa [18]. The antimicrobial capacity of i-PRF can be attributed to the presence of antibacterial factors, such as lysozyme, and the formation of a physical barrier that prevents bacterial proliferation [19]. This characteristic adds a significant benefit to the use of i-PRF in clinical applications, reducing the risk of infectious complications and enhancing its safety.

The antimicrobial properties of i-PRF can also be attributed to the presence of leukocytes, particularly neutrophils and lymphocytes, in its composition. These cellular elements act as immune sentinels, contributing to the elimination of invading pathogens and preventing the progression of potential infections at the i-PRF application site [20].

i-PRF as a Pharmacological Carrier

i-PRF has also demonstrated potential as a drug delivery system [21]. Due to its unique fibrin matrix structure, i-PRF can serve as a carrier and release platform for various therapeutic agents, such as antibiotics, anti-inflammatory drugs, and growth factors. This capability enables localized and sustained delivery of these agents to the target tissue, enhancing their therapeutic efficacy while minimizing systemic side effects [21-23]. The ability of i-PRF to function as a drug delivery system is a significant advantage, as it allows for the incorporation of tailored treatments specific to the patient's needs and the particular injury or condition being addressed.

A key advantage of i-PRF compared to PRP is its gradual and prolonged release of growth factors over time. While PRP releases growth factors within minutes to hours after application, i-PRF provides a much longer release, typically extended over a period of 14 days [24]. This is an advantage that makes i-PRF comparable to PRP, as even with a lower platelet concentration, it can release growth factors over a longer period, thereby promoting better regeneration.

The fibrin matrix of i-PRF functions as a scaffold that helps retain large and small molecules at the application site for an extended period. These molecules are considered potential tools capable of targeting specific sites to enhance the regeneration of bone and cartilage tissue [4].

Drawing an analogy between construction and regenerative medicine (**Figure 1**), one can imagine a worker laying bricks in a building. If this worker were surrounded by a network of reinforcement bars (scaffolding), they would have more difficulty moving freely within that area [25]. Consequently, they would end up performing their work gradually and sustainably, rather than in a rapid flow. This is due to the presence of the support structure (scaffolding), which metaphorically represents the fibrin network.

In the biological context of regenerative medicine, the worker would represent the therapeutic agent, while the reinforcement bars would symbolize the fibrin matrix, enabling the gradual and sustained release of the agent as a result of this scaffolding structure. Just as the worker's movements are restricted by the reinforcement bars, the fibrin matrix of i-PRF acts as a scaffold that helps retain large and small molecules at the application site for an extended period, resulting in the gradual and sustained release of therapeutic agents as a true and efficient drug delivery system [25].

Challenges and Limitations in Using i-PRF as a Pharmacological Carrier

Despite the great potential of i-PRF as a drug delivery system, several important issues need to be addressed. Among them is the stability of the drug within the fibrin matrix, which can be influenced by the biochemical properties of i-PRF. Furthermore, the precise control of the release rate of therapeutic agents presents a challenge, particularly given the complexity of interactions between the drug and the biological microenvironment [26]. Finally, potential interactions between the drug and the bioactive components of i-PRF, such as cytokines, growth factors, and cells, may impact both the drug's efficacy and the properties of i-PRF. These aspects highlight the need for further studies to optimize this application and ensure its clinical safety and efficacy.

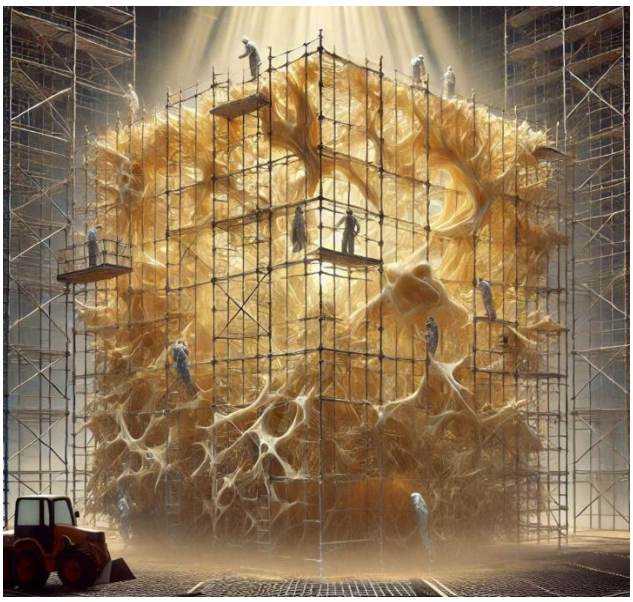

Figure 1: An Analogy Between Scaffolds and Biological Matrices in Regenerative Medicine

i-PRF in Bone Regeneration

The use of i-PRF has shown promising results in the field of bone regeneration. In vitro studies have demonstrated that i-PRF exhibits superior biological properties, including the ability of osteoblasts to proliferate, differentiate, and produce mineralized nodules more efficiently compared to other platelet-rich plasma formulations [27].

The application of i-PRF in combination with bone grafts and other bone augmentation techniques has shown significant beneficial effects. i-PRF acts as a potentiator of bone regeneration by stimulating the proliferation and differentiation of osteogenic cells, promoting revascularization, and accelerating the graft consolidation process [28].

Clinical studies have also demonstrated the potential of i-PRF in bone regeneration for various applications, such as maxillary sinus augmentation procedures, regeneration of post-extraction bone defects, and fracture repair [5]. In these studies, i-PRF has been shown to accelerate bone formation, increase the density and quality of newly formed bone, and improve the integration of bone grafts.

i-PRF in Cartilage Regeneration for Osteoarthritis

i-PRF significantly promotes chondrocyte proliferation and the mRNA levels of Sox9, type II collagen, and aggrecan when compared to PRP and the control group [29]. This beneficial effect of i-PRF on cartilage regeneration is attributed to its ability to induce the differentiation of mesenchymal stem cells into mature chondrocytes [30].

Furthermore, i-PRF has demonstrated a significant reduction in the levels of pro-inflammatory cytokines, such as interleukin-1β and tumor necrosis factor-α, in experimental models of osteoarthritis. Studies on knee osteoarthritis treatment indicate that i-PRF can reduce pain and improve joint functionality in patients, possibly due to its anti-inflammatory properties [31,32]. The improvement in pain and joint function observed in patients with knee osteoarthritis treated with i-PRF suggests that this product may be an effective therapeutic alternative for this clinical condition.

Thus, i-PRF emerges as a promising therapeutic alternative for the treatment of osteoarthritis, as it not only significantly stimulates cartilage regeneration but also exhibits potent anti-inflammatory effects that may contribute to pain reduction and substantial improvement in joint function [33]. This biological and clinical characteristic of i-PRF aligns it with the therapeutic effects and mechanisms of action of bone marrow aspirate, for example, but with less complexity in terms of extraction and application. This makes i-PRF a more accessible and convenient tool for physicians and patients with musculoskeletal disorders.

Thus, i-PRF stands out as an effective and attractive therapeutic option for managing osteoarthritis, combining its ability to regenerate cartilage with anti-inflammatory properties, which may represent a more comprehensive and effective approach to this debilitating clinical condition [32].

Aplicações clínicas do i-PRF

The use of platelet-rich plasma in the treatment of knee osteoarthritis and other joint conditions already has a solid foundation in clinical research and high-impact publications [34]. Several studies have demonstrated improvements in pain and joint function with the application of platelet-rich hemoderivatives in musculoskeletal conditions, particularly with the use of PRP. Regarding i-PRF, however, a preclinical study evaluated its effect on cultured chondrocytes and osteochondral regeneration in critical-sized osteochondral defects in rabbit knees, compared to PRP [35]. The results demonstrated that i-PRF significantly increased chondrocyte proliferation and the gene expression levels of chondrogenic markers, such as Sox9, type II collagen, and aggrecan, compared to PRP. Additionally, the use of i-PRF showed a significant reduction in the levels of pro-inflammatory cytokines, such as IL-1β and TNF-α, in experimental models of osteoarthritis. Regarding bone regeneration, the results indicated that both i-PRF and PRP were capable of promoting bone formation, with i-PRF showing superior performance in inducing osteochondral tissue regeneration [35].

Studies on i-PRF are still in their early stages, but the initial results are encouraging and highly promising. Several studies have successfully used solid PRF for cartilage repair [36]. Kemmochi et al. developed a method for using PRF in the repair of meniscal injuries [37]. They observed significant clinical and radiological improvement with the use of PRF compared to the control.

Cost-Effectiveness of i-PRF

i-PRF is an interesting alternative in terms of cost-effectiveness when compared to other platelet-rich plasma formulations [3,38]. The single centrifugation process, the ability to obtain a sufficient amount of product from a small blood sample, the reduced preparation time, and the simplicity of i-PRF preparation contribute to its potential to lower costs compared to other complex and expensive biological therapies. Although the initial costs of centrifuge equipment and the necessary materials for i-PRF preparation may require an upfront investment, the medium-term use of i-PRF can be economically advantageous compared to other therapeutic options. In addition to its low cost, the rapid preparation of i-PRF, the simplicity of the procedure, and the high availability of the patient's own blood sample further enhance its cost-effectiveness compared to other biological therapies [39,40].

In clinical practice, these characteristics make i-PRF one of the most viable and accessible biological products for patients and physicians, particularly in public healthcare settings and systems with limited resources. Such advantages facilitate the broader adoption of the method and the application of i-PRF, benefiting a larger number of patients with musculoskeletal and osteoarticular conditions. Ultimately, the favorable cost-effectiveness profile of i-PRF has the potential to expand the use of regenerative medicine.

Conclusion

The future prospects for the use of i-PRF in orthopedics are promising, particularly concerning its potential for regenerating musculoskeletal and joint tissues.

There are already different generations of PRF, such as A-PRF, T-PRF, and C-PRF. Each of these peripheral blood-derived products has unique physiological characteristics and growth factor release profiles, making them viable options not only in dentistry but also in other medical fields.

These options, considered evolutions of i-PRF, tend to behave differently from the standard product, offering new regenerative possibilities. All these next-generation products benefit from simplified preparation, high availability of blood samples, and low cost, with potential advantages in platelet concentration and increased release of cytokines and growth factors relevant to orthopedic applications.

Thus, it is expected that the refinement of peripheral blood concentrate formulations will further expand the use of regenerative medicine in orthopedics, providing increasingly effective, accessible, and tailored therapies for various conditions.

In summary, i-PRF appears to be an attractive option for biological therapy in terms of cost-effectiveness, owing to its low production cost and simplicity of collection and application, making it more accessible to patients compared to other more complex and expensive options.

Decelerations

Ethics approval and consent to participate

Not Applicable

Conflicts of Interest

There is no conflict of interest.

Funding Statement

None

Acknowledgement

None

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