DERLEME REVIEW

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A REVIEW OF THE ROLE OF PLATELET RICH FIBRIN IN HEALING AND REGENERATIVE PROCESS AND ITS USE IN ORTHOPAEDIC SURGERY

PLATELETTEN ZENGİN FİBRİNİN İYİLEŞME VE REJENERASYON SÜRECİNDEKİ ROLÜ VE ORTOPEDİK CERRAHİDE KULLANIMINA DAİR BİR DERLEME

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Öz

Plateletten zengin fibrin (PZF) doğal yollardan oluşan bir fibrin bazı ve ikinci-jenerasyon trombosit konsantresidir. Farklı büyüme faktörleri ve sitokinlerin sekresyonu, osteoblast adezyonunu kolaylaştırıcı etkisi ve kollajen protein ekspresyonunun artışı gibi fonksiyonları açısından yara iyileşmesi ve rejenerasyon sürecini tetikleyici potansiyeli büyüktür. PZF kullanımının ortopedik cerrahi alanındaki öneminden hareketle, bu derlemede PZF'nin iyileşme ve rejenerasyondaki rolü ve ortopedik cerrahideki kullanımı sunulmaktadır. Sonuç olarak, PZF klinik araştırmalara yeni bir boyut getiren ve ortopedik cerrahide kullanım alanı açısından geniş potansiyel vaad eden bir tedavi alternatifidir. Daha basit hazırlama protokolü, fizyolojik bir yapıda olmasını sağlayan daha güçlü ve stabil fibrin polimerizasyonu, daha esnek ve iyi fibrin ağını sağlayan doğal yollarla pıhtı oluşumu ve büyüme faktörleri ve sitokinlerin sürekli ve zaman içinde dengeli salınımı ile yara iyileşmesi ve rejenerasyon süreci fizyolojik kriterlerini karşılar görünmektedir.

Anahtar Kelimeler: Plateletten zengin fibrin; yara iyileşmesi, doku rejenerasyonu; büyüme faktörleri; ortopedik cerrahi

Abstract

Platelet-rich fibrin (PRF) is a naturally derived fibrin scaffold and second-generation platelet concentrate. It has great potential for promoting wound healing and the regenerative process via the secretion of different cytokines and growth factors, enhanced osteoblast adhesion, and augmentation of collagen protein expression. Given the significance of the scope of PRF in the field of orthopaedic surgery, this study presents an overview for the role of PRF in the recovery and the regenerative process with emphasis on use in orthopaedic surgery. In conclusion, PRF offers a new dimension for clinical research with expanded range of potential applications in orthopaedic surgery. It seems to have a simpler preparation protocol, a stronger and more stable fibrin polymerization leading to a physiologic architecture, occurrence of natural clot formation allowing formation of a flexible and fine fibrin network and a continual and steady release of cytokines and growth factors, mimicking the requirements of the reparative tissue and wound healing processes.

Keywords: Platelet rich fibrin; wound healing; tissue regeneration; growth factors; orthopaedic surgery

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Introductıon

Advances in surgical techniques and diagnostic imaging and implant optimization with autologous bone grafting are the main areas of progression to reduce morbidity and to improve patient outcomes in orthopaedic surgery (1,2). Accordingly, using regenerative and/or biological adjuncts to improve the recovery and tissue regeneration has become the latest interventional step (1,2).

Even though the autologous bone grafting is accepted as the gold standard repair method, it has been associated with the likelihood of postoperative haemorrhage, nerve injury and dysfunction complications as well as the risk of autograft failure (3). Accordingly, use of inert bone graft materials have become a more favourable option in management of bone defects, despite they act as a supporting material with a limited potential on skeletal regeneration (2,4).

Wound healing is a complex process involving many cellular responses, such as proliferation, inflammation, angiogenesis, migration, and tissue remodelling (5). On the basis of osteo-inductive and collagen synthetic properties, adding the derivatives of platelet to bone is considered to offer better results for grafting than bone alone (1,2,4,6-9). This leads to the use of platelet derivatives with a potential benefit in many challenging areas of orthopaedic surgery such as surgical repair of large bone defects, rotator cuff, meniscus, tendon, ligament, and articular cartilage (1,2,4,6-9).

The risk of cross-infection and difficulties in the preparation of fibrin adhesives provoked development of the platelet-rich plasma (PRP), while the platelet-rich fibrin (PRF) was developed via further simplification of the procedure and considered to involve all components for optimal recovery and healing (10).

As a naturally derived fibrin scaffold and a second-generation platelet concentrate prepared with a simplified method, PRF has a potential to catalyse wound healing, haemostasis, and the variation of pre-osteoblasts (2,8,11-15). It has been considered to have a role in promoting the healing and the regenerative process via secretion of different cytokines and growth factors, enhanced osteoblast adhesion, and augmentation of collagen protein expression (2,8,11-15). Accordingly, while platelet-derived products were in the clinical use as a source in regenerative medicine in various medical settings including dentistry, maxillofacial, orthopaedic, and ophthalmology, the scope of PRF is considered important in the orthopaedic surgery (8,16).

This study presents an overview for the role of PRF in the recovery and the regenerative process with emphasis on its use in orthopaedic surgery.

History Of Platelet Concentrates: From Fibrin Glues To PRP And PRF

Platelets play a crucial role in the tissue regeneration and coagulation phases of wound repair by releasing cytokines and growth factors stimulating the cell migration and proliferation, such as PDGF, TGF-ß, basic FGF (bFGF), IGF-1, epidermal growth factor (EGF), and hepatocyte growth factor (HGF) as well as different angiogenic and antiangiogenic proteins (8,17-19).

Platelet-derived factors is considered to have a great potential as biological therapeutics in regenerative medicine and they are widely used in clinical applications and surgical operations that require tissue regeneration (8,17,18,20,21).

Use of blood-derived technologies has started in the 60s to 70s with use of fibrin glues on skin healing (22), and followed by use of platelet-fibrinogen-thrombin mixtures (23), platelet-derived wound healing factors (24), platelet gels (25) and platelet concentrates including PRP and PRF (16,26-28). Hence, the technology has focused on 3 interconnected phases to date including first the fibrin matrix, then the growth factors, and currently the direct effects of cellular content (leukocytes and platelets) (26).

Platelet concentrates were initially developed based on utilizing a two-step centrifugation procedure and with use of anticoagulants, termed PRP (13,26,29-31). However, due to later findings on the adverse impact of anticoagulant addition on wound healing, PRF formulation was developed by utilizing platelet concentrates without using anti-coagulants in the preparation (13,26,29-31).

Currently, the generic name “PRF” has been used in the terminology instead of individual brand names, consistent with expanded range of its potential applications (13,30,32). However, PRF was in fact designated as the Pure Platelet-Rich Fibrin (P-PRF), Leukocyte- and Platelet-Rich Fibrin (LPRF), advanced PRF (A-PRF) and injectable PRF (i-PRF) as well as several other groups of products such as a novel liquid formulation of PRF (L-PRF) obtained via utilizing lower centrifugation protocols (13,30,32).

PRF in Healıng And Regenerative Process

PRP is generally considered as the enhanced fibrin glues, while PRF is the second-generation dense fibrin biomaterial (i.e. derivative of PRP) with advanced biomechanical characteristics that can serve as a biological healing matrix by supporting cell migration and cytokine release (11,16,30,32) (Table 1).

PRF has been associated with several advantages over the first generation PRP, such as simpler preparation protocol, easier application, lower cost and lack of biochemical modification (12,33). In addition, PRF has been associated with a stronger and more stable fibrin polymerization leading to a physiologic architecture that assists the healing process (8,26,34), and occurrence of natural clot formation with a natural platelet degranulation without the stimulation of thrombin, allowing the formation of a fine and flexible fibrin network that support cellular migration and cytokine release (8,11,12,35). Moreover, it is a real biomaterial involving platelets, fibrin clot, and leukocytes acting to promote local wound healing and fight off the infection (11,13,16) (Table 1).

In contrast to rapid polymerization process in the presence of high thrombin concentration and thus, the rapid release of proteins from PRP in a day, slow and natural polymerization in PRF enables a continual and steady release of growth factors and cytokines from the fibrin graft in a 10-day period (12,36,37).
Accordingly, PRF is the only autologous fibrin matrix with scaffolding properties, which releases growth factors continuously and slowly (17,38-40), fulfils the 3 main criteria of acting as a scaffold, and contain living cells and growth factors simultaneously (13,29). Thus, PRF is the ideal source of components for the recovery period with abundance of three main platelet cytokines (TGFβ-1, PDGF-BB, and IGF-1) (40-42) and a high potential for tissue repair that suits better to long-term release (12).

Use Of PRF in Orthopaedıc Surgery

The rationale for use

Original PRF is a gelatinous solid body that allows the use of PRF in orthopaedic surgery either directly as a bell-shaped clot (PRF matrix) or as a strong membrane after compression (PRF membrane) (40). PRF has been shown to be associated with an increase in osteoblast attachment and with proliferation and up-regulation of collagen-related protein production in in vitro quality assessment studies (12,14,43-46). Alongside its advanced biomechanical properties, this indicates its great potential to effectively promote bone regeneration (12,14,43-46).

In addition to simplified processing technique with high reproducibility and appropriate firmness for maintenance of the shape during the orthopaedics surgery, utility of PRF and advantages over standard repair procedures in terms of wound healing, bone regeneration, graft stabilization and wound sealing has been shown in various orthopaedic surgical situations (40,47-50).

Notably, in a systematic review of 48 studies regarding the application of PRF for the soft tissue regeneration, augmentation and or wound healing, authors concluded PRF usage to be advantageous in 85%

Table 1 Comparison between platelet concentrates (16)

Characteristics	Fibrin glue	PRP	PRF
Purely autologous			+
No biochemical modification of blood			+
Cost effective			+
Preparation requires anti-coagulants	+	+	
Wound healing	+	+	+
Regenerative potential		+	+
Release of growth factors	+	+	+
Haemostatic properties	+	+	+
Supportive role in immune system			+
Most efficient cell migration and proliferation			+
Continual and steady release of growth factors			+

PRP: Platelet-rich plasma; PRF: Platelet-rich fibrin
Adapted from Nanditha S, et al. Appraising the diverse facets of Platelet rich fibrin in surgery through a systematic review. Int J Surg. 2017;46:186-194 (16).

of the in-vitro and 100% of the in-vivo studies, while positive wound healing was shown with PRF usage in 58% of the clinical studies and 87% of the clinical studies defended the application of PRF for soft tissue regeneration and wound healing for different surgical operations (29).

Large variations in the preparation and administration methods are considered associated with inconsistency regarding the clinical outcomes of platelet concentrate therapies in orthopaedic surgery (51). In this regard, besides being a less extensively studied area than PRP, investigations addressing use of PRF in orthopaedic surgery revealed inconsistent data on the clinical outcomes (51).

Composition of platelet concentrate, localization of platelet concentrate to the target region and duration of in situ therapeutic effectiveness are considered factors associated with efficacy of treatment (51). Nonetheless, amongst the three major types of delivery (injection, invasive implantation, and topical application) for platelet concentrates, use of PRF is based on intraoperative implantation and platelet concentrates in solid form (PRF) is considered superior to liquid PRP in terms of localization to the lesion sites (52). However, the amount of growth factors released over time and the manufacturing process of the different platelet-rich preparations and an immense inter-individual variation in the quantity and quality of platelets and growth factors leads to variability in efficacy of PRF with a wide variation in platelet activation, growth factor release, and reaction with the cells of the tendon and bone (38,53,54)

Treatment Outcomes

The use of solid scaffolds for the long-term delivery of growth factors is a novel approach, particularly the use of L-PRF as a regenerative in situ tissue engineering method during the treatment of tendinopathies of the quadriceps and the patellar tendon and for regenerative stimulation in rotator cuff repair or in anterior cruciate ligament repair (7).

In particular, use of PRF in experimental and clinical studies revealed favourable outcomes in articular cartilage defects (12,55-57), meniscal repair (58), knee arthroplasty (59,60), healing in tendinopathies (6,26,48,61,62), rotator cuff repair (26,63-66) and augmentation of anterior cruciate ligament (26,52).

Articular Cartilage Defects

Cartilage transplantation to the medial femoral condyle with PRF augmentation in a porcine model of osteochondral defects was shown to be associated with better matrix, cell distribution and cartilage mineralization than use of cartilage fragments or RF alone (12). Authors indicated positive effect of PRF on the cartilage repair when combined with autologous chondrocytes, emphasizing the likelihood of a successfully employed technique to target cartilage defects in vivo (12). In an in vitro and ex vivo analysis of the chemotactic effects of PRF on chondrocytes harvested from the primary culture of rabbit cartilage, combining PRF and autologous cartilage graft for repairing articular chondral defects was reported to be associated with capacity for cartilage repair in terms of its positive effects on the migration, proliferation, viability and differentiation of chondrocytes (56). Authors emphasized the likelihood of PRF to simplify and potentiate the efficacy of autologous cartilage transplantation in clinical practice (56).

Use of intraoperative PRF vs. postoperative PRP or no platelet concentration in patients undergoing micro-fracturing for knee pain related to cartilage lesions was reported to be associated with better clinical results at an earlier period of 2 year follow up in terms of clinical scores (IKDC, VAS pain) and MRI-based MOCART criteria (55).

Transplantation of autologous bone marrow mesenchymal stem cells (BM-MSC) on platelet-rich fibrin glue (PR-FG) as a cell scaffold was reported to an effective approach to promote the repair of full-thickness articular cartilage defects of the knee, particularly in patients with large-sized defects (>4 cm2) (57). Authors concluded the 1-year clinical outcomes support the efficacy of PR-FG in fixing the cultured MSCs within the defects and enabling a suitable environment for the synthesis of a hyaline-like cartilaginous matrix (57).

Meniscal Repair

Low thrombin level of PRF has been considered optimal for the migration of endothelial cells and fibroblasts and thus for the promotion of angiogenesis, which is of critical importance for meniscal healing (58,67). However, role of PRF as a bioactive scaffold in facilitating meniscal repair has been addressed only in few studies (58). Positive anabolic effects of PRF on meniscocytes harvested from the primary culture of a rabbit meniscus were reported in vitro in terms of cell migration, proliferation, and extracellular matrix formation (58). In addition, efficacy of PRF on facilitation of meniscal repair was shown in a rabbit model of meniscal defects with significantly improved quality of meniscal healing noted in the PRF-augmented suture vs. non-suture or suture-only groups (58). Hence, the potential utility of PRF-based therapeutic approach has been suggested in augmenting the healing of meniscal injuries in clinical practice (58).

Tendinopathies

In a retrospective analysis of patients undergoing surgery for acute rupture of the Achilles tendon with and without PRF augmentation, gait analysis 6 months after surgery revealed significant functional improvements in term of biomechanical characteristics and efficiency of motion during the gait cycle in the PRF group (6). Authors also emphasized the potential efficacy of PRF to support tendon healing, reconstruct tendon extension and flexible return and potency of muscle work during ambulation at the sixth postoperative month, compared with surgical repair only (6). PRF has also been associated with a higher likelihood of improvement and acceleration of healing when compared to PRP in an animal model of Achilles tendon repair (48).

In a retrospective analysis of the effect of PRF matrix (PRFM) on outcomes after surgical repair of gluteus medius tendons, PRFM augmentation had no positive effect on pain or clinical evidence of re-tears, while the likelihood of its association with improved subjective outcomes of overall and hip-specific physical functioning was considered (68).

PRF scaffold is suggested to have a potential to accelerate healing of tendons and ligaments in rabbit models of patellar tendon and medial collateral ligament defects as a provisional bioscaffold or a material for graft augmentation (61). In a dog model of patellar tendon defect, PRF membrane was not associated with an improvement in the rate or quality of tendon healing, whereas resulted in an increased amount of repair tissue within and surrounding the defect, suggesting that a PRF membrane may not be indicated for augmenting the repair of acutely injured tendons that are otherwise healthy (62).

Hence, PRF matrices seem to play a central role in the complex processes of tendon healing (6) and it is possible to suggest the use of PRF may be a promising alternative in orthopaedic surgery, although further experiments are required to support published results (48).

Rotator Cuff Tear

Given the association of PRF, unlike other platelet concentrates, with progressive release of cytokines during fibrin matrix remodelling, application of growth factor mixtures through PRF maps is considered a potential approach for tendon-bone insertion regeneration such as rotator cuff repair (64). Accordingly, suturing PRF side-to-side to close the tear in patients with rotator cuff tear was reported to be associated with improved range of motion and pain relief alongside the decrease in the re-tear rates (65,66). Local application of autologous PRF to the repair site of massive rotator cuffs was shown to be associated with improved functional outcome and integrity of the arthroscopically repaired tendons than a standard repair (63).
However arthroscopic rotator cuff repair with local application of L-PRF to the repair site was also reported be associated with no beneficial effect in clinical outcome, anatomic healing rate, mean postoperative defect size and tendon quality at 12 months of follow-up (54). Similarly use of leucocyte-poor or P-PRF for rotator cuff augmentation was not associated with superior clinical and structural outcomes compared with a control group (69,70), or associated with lower healing defect rates without a clinical difference in outcome measures (71) in other studies.

In a systematic review of randomized controlled trials on patient outcomes in arthroscopic rotator cuff repair, it was concluded that in contrast to PRP, PRF was not associated with improved healing rates, pain levels, and functional outcomes (72), while in a meta-analysis on the efficacy and safety of PRF in improving clinical outcomes in rotator cuff tears, it was concluded that PRF does not have better effect on improving the overall clinical outcomes and re-tear rate in the arthroscopic repair of rotator cuff tears (64).

While the exact mechanism underlying failure of PRF to fulfil its promise remains un known, some factors have been considered responsible for this failure such as inter-individual variations in growth factors contained in autologous source PRF that likely to affect the therapeutic effect of PRF as well as lack of enough data to determine the best clinical usage of PRF (64).
Anterior cruciate ligament (ACL) surgery

While the ACL rupture is the most common complete ligamentous injury in the knee and several studies investigated ACL graft integration and maturation, application of PRFM as augmentation for ACL reconstruction has only been assessed in a few studies (52).

In patients who underwent ACL reconstruction with semitendinosus and gracilis grafts with or without PRFM augmentation, assessment of graft-bone integration, knee stability and patient-reported functional status revealed similar outcome between groups in terms of radiologic graft integration and knee stability at 1 year from surgery, whereas better short-term improvement of patient-reported knee function (52).

Conclusıon

The therapeutic use of autologous PRF is a relatively novel biotechnology with remarkable potential in the agitation and speedup of the bone and soft-tissue healing (16,26). Simpler preparation protocol, easier application, lower cost, lack of biochemical modification, a stronger and more stable fibrin polymerization leading to a physiologic architecture and occurrence of natural clot formation allowing formation of a fine and flexible fibrin network seems to be major advantages of PRF (8,11,12,26,33-35).

On the basis of clinical and experimental evidence, the potential utility of PRF-based therapeutic approach has been suggested in simplifying and potentiating the efficacy of autologous cartilage transplantation (56), in augmenting the healing of meniscal injuries (58) and in improving tendon healing (6), while results on its impact on clinical outcomes in arthroscopic rotator cuff repair are inconsistent (64,72).

Composition of platelet concentrate, localization of platelet concentrate to the target region and duration of in situ therapeutic effectiveness are considered factors associated with efficacy of treatment with platelet concentrates (51). In general, treatments with intraoperative delivery of solid form of platelet concentrates (PRF) are considered more effective, while injections into anatomical sites with confined space to retain PRP are associated with consistent outcomes in orthopaedic surgery (51).

However, large variations in the preparation and administration methods, the amount of growth factors released over time and an immense inter-individual variation in the quantity and quality of platelets and growth factors leads to variability in efficacy of PRF (38,51,53,54). Nonetheless, PRF is considered to be the only autologous fibrin matrix that meets the 3 main criteria of acting as a scaffold, containing living cells, and containing growth factors, simultaneously (13,29). Consequently, PRF offers a new aspect for clinical studies with expanded range of potential applications in orthopaedic surgery, while further long-term studies need to determine the ideal composition of platelet and leukocyte concentration, fibrin architecture, and biological signature specifically in distinct areas of clinical applications to conclude an evidence-based effectiveness of PRF (16,26).

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