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Role of Platelet Concentrates in Periodontal Regeneration: A review

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KEYWORDS

Platelet rich fibrin (PRF), Periodontal regeneration, Platelet rich plasma (PRP), Concentrated growth factors.

ABSTRACT:

Platelet concentrates, including Platelet-Rich Plasma (PRP), Platelet-Rich Fibrin (PRF), and Concentrated Growth Factor (CGF), have emerged as promising adjuncts in periodontal regeneration due to their ability to enhance tissue healing and regeneration. These autologous biomaterials, derived from a patient's own blood, are rich in growth factors, cytokines, and platelets that play a crucial role in wound healing, tissue repair, and cellular regeneration. In periodontal therapy, platelet concentrates are used to promote regeneration of both soft and hard tissues, offering significant benefits in treating periodontal defects, bone loss, and gingival recession.

The role of platelet concentrates in periodontal regeneration is attributed to their ability to stimulate cellular activities such as proliferation, differentiation, and angiogenesis, which are essential for tissue repair and regeneration. PRP and PRF have been widely utilized in periodontal surgeries, including guided tissue regeneration (GTR), bone grafting, and soft tissue augmentation. These concentrates enhance the healing of periodontal defects, improve bone regeneration, and reduce inflammation, leading to faster recovery and better clinical outcomes.

Research has shown that platelet concentrates contribute to increased bone volume, improved attachment levels, and enhanced gingival tissue regeneration in periodontal treatments. Their minimal invasiveness, autologous nature, and ease of preparation make them a cost-effective and safe alternative to synthetic regenerative materials. The application of platelet concentrates represents a significant advancement in regenerative periodontal therapy, offering promising results for long-term improvements in periodontal health and patient outcomes.

1. Introduction

The goal of periodontal therapy is to eliminate inflammation, prevent disease progression, and regenerate lost tissues. While current regenerative procedures, such as grafts and guided tissue regeneration, can only partially restore tissue volume, platelet concentrates like platelet-rich plasma (PRP) and platelet-rich fibrin (PRF) have shown promise in accelerating healing by increasing growth factors (TGF-β, PDGF, VEGF, IGF-1) that support tissue regeneration. Developed in 2001, PRF is a second-generation concentrate that enhances healing by promoting cell migration and matrix formation. [1]

Platelet-rich fibrin (PRF), developed by Choukroun et al., is a second-generation platelet concentrate derived from the patient's own blood, without anticoagulants or artificial modifications. It forms a strong fibrin matrix that concentrates platelets and growth factors, enhancing tissue healing and regeneration. PRF accelerates wound healing more effectively than traditional methods and is superior to PRP due to its simplicity, cost-effectiveness, and lack of exogenous compounds. Additionally, PRF eliminates the need for a second surgical site, making it more advantageous than autogenous grafts. [2].

2. Historical background

Platelet concentrates, introduced in the 1970s, were created by mixing donor plasma with thrombin and calcium, leading to the polymerization of fibrinogen. However, this technique suffered from poor stability and posed a risk of disease transmission, particularly in

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commercially available products. In 1994, Tayapongsak proposed the use of autologous fibrin glue, where blood was collected 1 to 3 weeks before the procedure and processed for 30 minutes to 48 hours using methods such as ammonium sulphate precipitation or the cryo-precipitate technique. Despite its innovation, the technique was lengthy and complex, yielding a small amount of concentrate relative to the blood collected (2 ml from 75 ml of blood in ammonium sulphate technique, and 10-15 ml from 250 ml of blood). In 1997, Whitman introduced Platelet Rich Plasma (PRP), which involved double centrifugation of autologous blood with an anticoagulant which separates the blood into components. After a soft spin, the buffy coat and plasma are re-centrifuged, and PRP is collected at the bottom. However, the use of bovine thrombin in this method could, in rare cases, cause life-threatening coagulopathies. Two years later, in 1999, Anitua and colleagues developed Plasma Rich in Growth Factors (PRGF), which required centrifuging anti- coagulated autologous blood at 460G for 8 minutes, then adding $CaCl_2$ to induce coagulation, resulting in a gelatinous PRGF after about 10 minutes. This technique, however, often led to incomplete platelet activation and a low release of growth factors. Finally, in 2001, Joseph Choukroun introduced Platelet Rich Fibrin (PRF), where blood was collected in sterile tubes without anticoagulant and centrifuged at 3,000 RPM for 10 minutes. This process formed a structured fibrin clot between the red blood cells and acellular plasma. A stable fibrin membrane was obtained by squeezing serum from the PRF clot. Unlike other platelet concentrates, slow fibrin polymerization during PRF processing incorporates platelet cytokines and glycan chains into the fibrin mesh, allowing PRF to progressively release cytokines during matrix remodelling, unlike other platelet concentrates. [3]

3. Platelet concentrates

A) Platelet rich plasma:

Platelet-rich plasma (PRP) concentrates, used primarily for severe thrombocytopenia, are created by double centrifugation to increase platelet concentration. In surgical applications, PRP refers to platelet concentrates created by double centrifugation to increase platelet concentration.

To clarify the term, "cPRP" (concentrated platelet-rich plasma) is suggested. cPRP is activated with thrombin and calcium chloride to release growth factors that promote healing.

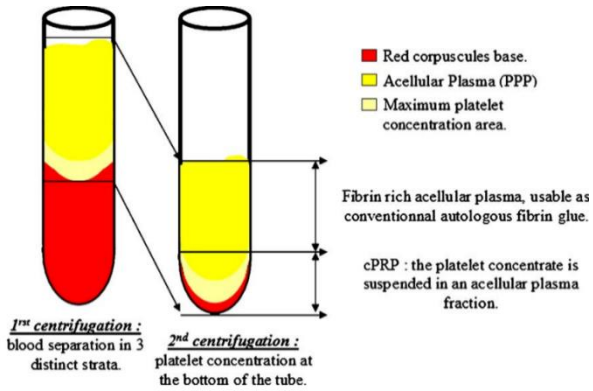

Fig-1: Technologic concept of cPRP processing

The cPRP process generally follows these steps:

(1) Blood is collected with an anticoagulant to prevent platelet activation.

(2) A "soft spin" centrifugation separates the blood into three layers: red blood cells at the bottom, platelet-poor plasma (PPP) at the top, and an intermediate "buffy coat" containing concentrated platelets.

(3) The practitioner aspirates the PPP and PRP layers, transferring them to a second tube without anticoagulant.

(4) A "hard spin" further concentrates the platelets, resulting in three distinct layers: residual red blood cells, PPP, and a buffy layer of platelet-rich plasma (PAP).

(5) PRP is collected by discarding most of the PPP, leaving a suspension of concentrated platelets.

(6) cPRP is mixed with thrombin and calcium chloride to form a gel, which can be applied as a gel or spray. Fibrinogen polymerization creates a fibrin matrix with haemostatic and adhesive properties, and Tisseel can be added for a denser gel or membrane. [4]

Growth Factors Present: PRP is a concentrated suspension of growth factors from platelets that enhance wound healing, tissue repair, and bone regeneration. These growth factors work together to enhance healing process and promote tissue regeneration in periodontal and bone defects.

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Key growth factors in PRP include:

• Platelet Derived Growth Factor (PDGF): Stimulates cell replication and angiogenesis, aiding in connective tissue and bone healing.

• Transforming Growth Factor (TGF): Promotes cell differentiation and matrix formation, influencing osteoblasts and fibroblasts for tissue regeneration.

• Insulin Growth Factor (IGF): Stimulates proliferation and differentiation of osteoblasts, aiding in bone formation and periodontal ligament regeneration.

• Epidermal Growth Factor (EGF): Facilitates cell differentiation, angiogenesis, and collagen production, promoting wound healing and tissue repair.

• Vascular Endothelial Growth Factor (VEGF): Stimulates angiogenesis, enhancing blood vessel formation and tissue regeneration. [5]

Role of PRP in Periodontal Regeneration:

• Regenerative procedures are crucial for periodontal and bone regeneration, especially for dental implant placement. PRP enhances bone graft maturation by up to 2.16 times and improves soft tissue healing by increasing collagen, promoting angiogenesis, and strengthening early wound healing.

• During bone grafting, platelets release PDGF and TGF-β, stimulating capillary growth and osteoblast activity.

• Macrophages, attracted by an oxygen gradient, drive the healing process.

• Platelet lifespan is <5 days, but bone regeneration is extended through stem cell differentiation into osteoblasts and macrophage replacement.

• By day 14, complete vascularization occurs, leading to woven bone formation at 4-6 weeks, followed by lamellar bone and functional maturation.

• PGDF is a chemo attractant for fibroblasts, leukocytes, and smooth muscle cells, it promotes protein synthesis, extracellular matrix formation, and collagenase activity & acts synergistically with IGF-1 to enhance tissue regeneration.

• TGF-β induces synthesis of fibronectin, collagens (Type I, III, V), and metalloproteinase inhibitors. It stimulates osteoblast activity, aiding bone regeneration. [6, 7]

Advantages:

• Soft autologous preparation, free from concerns over transmissible disease such as HIV, hepatitis etc.

• Convenient for patient, blood is collected in the immediate preoperative period.

• Presence of platelets brings cytokines and growth factors to the site of surgery which helps in rapid regeneration in a manner that would not occur with fibrin glue.

Disadvantages:

• Concern over the use of bovine thrombin, the fact that bovine thrombin has been associated with development of antibodies to clotting factors V, XI and thrombin, which had occasionally lead to life threatening coagulopathies.

• Lack of uniformity in PRP preparation protocol as different platelet concentration has different storage time. [8]

B) Plasma rich in growth factors

PRGF is a platelet concentrate preparation that is less time-consuming, does not require bovine thromboplastin, and uses less blood. It produces both PRGF and a fibrin membrane in a single step. PRGF contains various growth factors like TGF, PDGF, VEGF, EGF, bFGF, and PAF-4, which support bone and soft tissue regeneration. It aids in wound healing by forming clots and releasing growth factors, without the need for bovine or human thrombin for coagulation.

C) Plasma rich fibrin

Platelet-rich fibrin (PRF) is an immune and platelet concentrate collecting on a single fibrin membrane all the constituents of a blood sample favourable to healing and immunity. Though platelet and leukocyte cytokines play an important part in the biology of this biomaterial, the fibrin matrix supporting them certainly constitutes the determining element responsible for the real therapeutic potential of PRF. [9, 10]

Development of PRF from PRP: In the early 2000s, Joseph Choukroun developed PRF (platelet-rich fibrin) as a second-generation concentrate using a simplified centrifugation process without anticoagulants. PRF forms a fibrin scaffold with macrophages and

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neutrophils, aiding early wound healing by clearing debris and promoting tissue regeneration. [4]

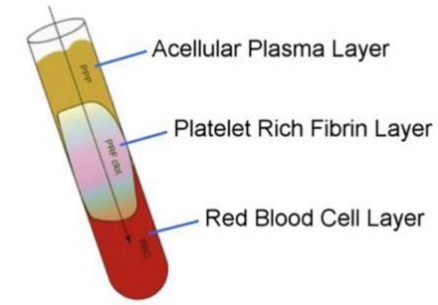

Fig-2:- Layers of PRF

Application of Platelet Rich Fibrin (PRF) in dental field:

(1) Sinus elevations procedures with PRF

PRF is used in sinus elevation procedures as a grafting material, for repairing the Schneiderian membrane, and to close the window in the lateral sinus approach. It is a cost-effective biomaterial that supports early soft tissue healing around implants.

(2) PRF for soft-tissue root coverage

PRF has been shown to aid soft-tissue regeneration, with over a dozen randomized clinical studies focusing on its use in periodontal surgery for Miller Class I and II muco-gingival defects.

(3) PRF for periodontal regeneration

PRF is being increasingly studied for regenerating intrabony and furcation defects in periodontics. As a safe, natural, and low-cost option, it has been compared in clinical trials to open flap debridement and other treatments like enamel matrix derivative (EMD). Results show significant improvements in periodontal pocket depth reduction and clinical attachment level gains with PRF-based regenerative therapy.

(4) PRF around dental implants

PRF aids both soft and hard tissue healing during implant placement. It enhances soft-tissue healing and augmentation when placed in soft-tissue flaps, and, when compressed into membranes, supports site protection and integrity during augmentation. PRF also promotes healing of the overlying flap, potentially reducing peri-implantitis risks.

(5) PRF in guided bone regeneration

PRF is commonly used in combination with bone augmentation procedures, enhancing vascular supply and graft stability. It has become widely utilized in dentistry for various procedures, initially as a scaffold matrix with other biomaterials. Over time, significant insights have been gained regarding PRF's regenerative potential and its effects on oral tissues. [11, 12, 13]

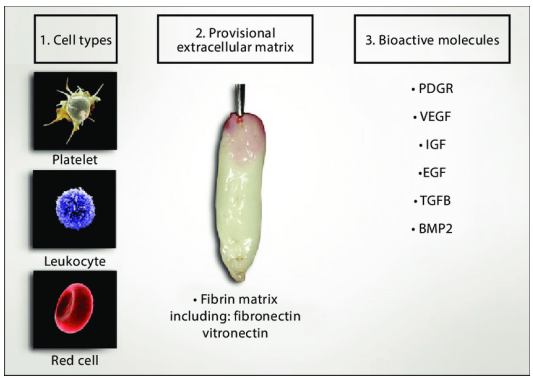

Fig. 3:- PRF consists of (1) cell types (platelets, leukocytes, red blood cells), (2) a provisional extracellular matrix scaffold made of autologous fibrin, and (3) over 100 bioactive molecules, including PDGF, VEGF, IGF, EGF, TGF-beta, and BMP2.

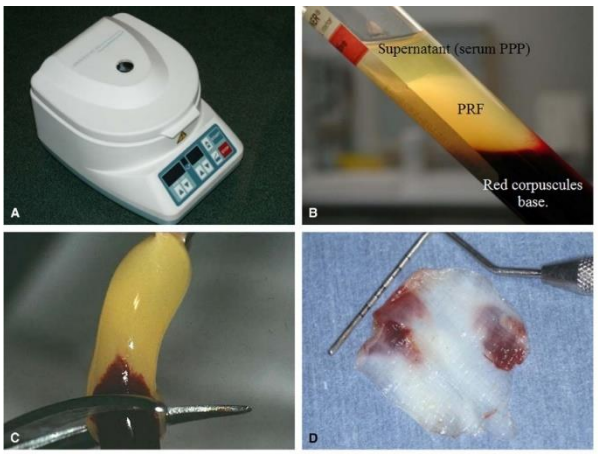

Fig.4: Blood processing with a PC-02 centrifuge for PRF (A; Process, Nice, France) allows the composition of a structured fibrin clot in the middle of the tube, just between the red corpuscles at the bottom and acellular plasma at the top (B). After collection of the PRF itself (C), resistant autologous fibrin membranes are easily obtained by driving out the serum from the clot (D).

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Advantages:

• Lack of biochemical modification

• Simplified and cost effective process

• Long term effect able to support cytokines enmeshment and cellular migration

• Increased incorporation of the circulating cytokines in the fibrin meshes (intrinsic cytokines)

• It is an immune organizing node supports and accelerates the healing process due to slow polymerization

• Helps in haemostasis

• Three dimensional structure gives elasticity and flexibility to PRF membrane

Disadvantages:

• Low quantity of PRF is obtained because of autologous blood so application in general surgery is limited

• The clinical benefit of PRF depends on time interval between speed of handling between blood collection and centrifugation as PRF is prepared without any addition anticoagulants

• The fibrin matrix contains the circulating immune cells and all the highly antigenic plasmatic molecules, that is why PRF is totally specific to the donor

• PRF membrane should be used immediately after preparation as it will shrink resulting in dehydration altering the structural integrity of PRF and leukocyte viability will be adversely affected altering its biologic properties

• PRF when stored in refrigerator can result in risk contamination of bacterial contamination

Major modifications of the PRF technique:

They have been suggested in the protocol over the last few years on the basis of centrifugation, time and low speed centrifugation concept: Choukroun J. (2017). They are:

• Leukocyte Platelet Rich Fibrin (L-PRF) was described by Choukroun in 2001, using 3000/2700 RPM for 10/12 minutes at 708g in glass-coated tubes.

• Concentrated Growth Factor (CGF) was introduced by Sacco in 2006, with an RPM range of 2400–2700 for 12 minutes.

• Sticky Bone, proposed by Sohn et al. in 2010.

• Titanium Platelet Rich Fibrin (T-PRF) was described by Mustafa Tunali in 2012, using 2800 RPM for 12 minutes in titanium tubes.

• Advanced Platelet Rich Fibrin (A-PRF) was introduced by Ghanaati in 2014, using 1500 RPM for 14 minutes at 208g in a patented tube.

• Advanced Platelet Rich Fibrin Plus (A-PRF+) was described by Fujioka-Kobayashi and Miron in 2016, using 1300 RPM for 8 minutes at 208g in the same tube type as A-PRF.

• Injectable Platelet Rich Fibrin (i-PRF) was introduced by Mourão in 2015, using 700 RPM for 3 minutes at 60g in non-coated tubes. [2]

Growth factors (GF) present in PRF and their functions:

• Transforming Growth Factor-(TGF-β): Stimulates proliferation of osteoblasts, synthesis of collagen type I and fibronectin, enhances woven bone formation, enhances chemotaxis of osteoblast cells, and stimulates angiogenesis.

• Platelet-Derived Growth Factor (PDGF): Migration and proliferation of mesenchymal lineage cells, angiogenic effect on endothelial cells.

• Vascular Endothelial Growth Factor (VEGF): Initiates angiogenesis

• Insulin Growth Factor-1 (IGF-1): Stimulates osteoblast proliferation, chemotactic effects towards human osteoblasts, increased expression of osteocalcin, enhances wound healing

• Epidermal growth factor (EGF): Stimulation of cell proliferation and extracellular matrix turnover, chemotactic effect on periodontal fibroblast cells. [5]

PRP vs PRF for growth factor release:

The development of PRF enables controlled, gradual release of growth factors, enriched by leukocytes within the fibrin matrix, enhancing tissue regeneration. Studies by Kobayashi et al. showed that PRF (L-PRF and A-PRF) released more growth factors over a 10-day period compared to PRP. [3, 14]

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D) Titanium Platelet Rich Fibrin (T-PRF)

It is established it as a new platelet product that induced new connective tissue to form in as little as 15 days with excellent regenerative potential. T-PRF used alone as a membrane formed new bone with connective tissue in the wound healing model of connective tissue, in which regeneration was not expected.

Titanium also pays a unique property of osseointegration, connecting both structurally and functionary with the underlying bone, and is commonly used in total joint replacements, dental implants, internal and external fixators, artificial heart valves, spinal fusion, and medical devices.

These results could lead to additional T-PRF animal and human studies of T-PRF in oral and maxillofacial surgery, implantology, and periodontology, and contribute to the understanding of this new platelet-rich product. [11, 15]

E) Advanced Platelet Rich Fibrin (A-PRF)

Leukocyte PRF (L-PRF) is prepared at 2700 rpm for 12 minutes in glass-based plastic tubes, while A-PRF is created at a slower speed (1500 rpm) for 14 minutes in plain glass-based vacuum tubes. The A-PRF protocol is believed to result in better platelet, neutrophil, and lymphocyte distribution, and higher numbers of viable cells, leading to increased growth factor and cytokine release.

However, some studies have shown contradictory results, with A-PRF releasing fewer growth factors compared to L-PRF. Further research is needed to fully compare the benefits and limitations of L-PRF and A-PRF. [16]

F) Injectable PRF (i-PRF)

Injectable PRF (*i*-PRF) is a recent advancement in PRF technology, offering a liquid form compared to the gel form of traditional PRF.

Unlike PRP, which is commonly used in various medical applications, PRF provides sustained release of growth factors over 7-21 days, promoting better cell proliferation and differentiation. *i*- PRF is produced by centrifuging blood without anticoagulants at low speeds (700-2700 rpm for 2-3 minutes), resulting in a light yellow supernatant that contains concentrated growth factors.

This liquid form can be mixed with bone grafts, forming a gel-putty consistency that improves graft handling and reduces graft leaching. *i*-PRF eliminates the risks associated with bovine thrombin and offers a promising alternative to PRP in various regenerative applications. [17, 18]

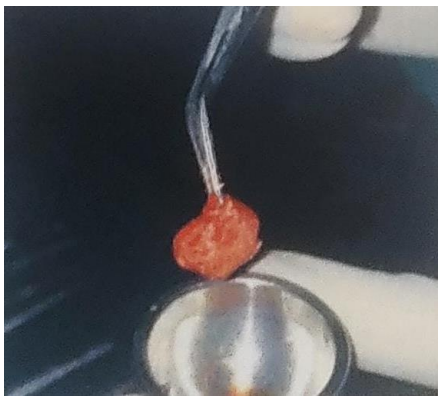


Fig.5: i-PRF mixed with bone graft forms a workable mass

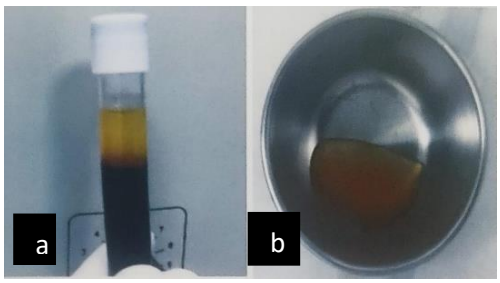
I-PRF obtaining method:

• To obtain i-PRF, blood was collected in 9 ml dry tubes (Biocon®, Brazil) without additives.

• After collecting three tubes, they were centrifuged for 2 minutes at 3300 rpm in a horizontal centrifuge (B-40, RDE®, Brazil), with a water-filled tube for balance.

• The process resulted in an orange-colored i-PRF layer, with remaining blood components below.

• The i-PRF was then carefully collected using a 20 ml syringe (Injex®, Brazil) with an 18G needle (Injex®, Brazil). [19, 20]



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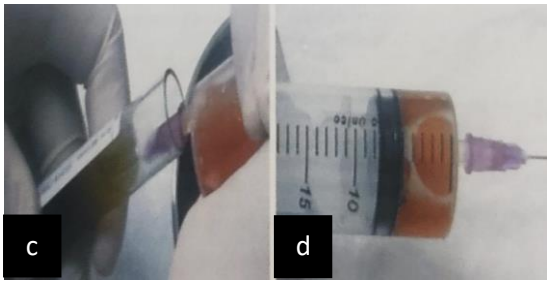

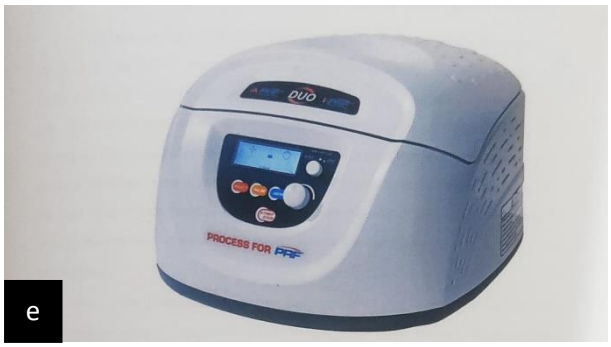

Fig.6 a: i-PRF obtained after centrifugation, b: I-PRF dispensed in the metal tank, c: i-PRF collection in the tube collecting from the tubes, d: Five millilitres of i-PRF obtained after centrifugation e: PRF Duo Centrifuge, (Process for PRF, Nice, France).

Advantages:

• This has the potential to convert any osteoconductive graft to osteopromotive (due to the presence of platelets & growth factors) which would translate into faster and better efficiency of bone formation.

• Release of the factors at the end of ten days was significantly higher in i-PRF.

G) Advanced Platelet Rich Fibrin+ (A-PRF+)

A modification of A-PRF+, proposed by Fujioka-Kobayashi et al. in 2016, reduces centrifugation to 1300 rpm for 8 minutes. This lower speed decreases the forces on blood cells, increasing the number of cells in the PRF matrix.

Their study found that A-PRF+ released higher levels of PDGF, TGF-β1, EGF, and IGF compared to L-PRF and A-PRF. Gingival fibroblasts exposed to A-PRF+ showed higher levels of PDGF, TGF-β, and collagen-1.

Lower centrifugation speeds improved platelet distribution, enhanced neutrophil entrapment, and increased macrophage differentiation, leading to better growth factor release and cellular response. [21, 22]

Advantage:

• A-PRF+ demonstrated highest release of PDGF, TGF-β1, EGF and IGF

4. Platelet rich fibrin and periodontal regeneration

True periodontal regeneration involves the regeneration of the periodontal ligament with Sharpey's fibres attaching to the alveolar bone and cementum. Platelet-Rich Fibrin (PRF) is a highly effective biomaterial in periodontal regeneration, derived from the patient's own blood.

The growth factors within PRF, such as PDGF, TGF-β, and VEGF, aid in cell proliferation, differentiation, and angiogenesis, all of which are vital for effective tissue healing. The fibrin matrix in PRF provides a scaffold for cell attachment and ensures sustained growth factor release. In the context of periodontal regeneration, PRF promotes the regeneration of bone, periodontal ligament, and cementum, facilitating the repair of periodontal tissues lost due to disease. It encourages the migration and differentiation of osteoblasts for bone formation, while also supporting fibroblast activity for soft tissue repair, reducing scar tissue formation and promoting healthy gingival healing.

It is commonly used in combination with techniques like guided tissue regeneration and bone grafts, making it a valuable adjunct in treating periodontal defects and promoting both hard and soft tissue regeneration. PRF has been studied in randomized clinical trials for regenerating periodontal intrabony and furcation defects showing improvements in pocket depths and clinical attachment levels.

Since PRF is autologous it carries no risk of immune rejection or disease transmission. PRF has been shown to have anti-inflammatory properties, which can help reduce the risk of infection and accelerate healing. [23, 24]

5. Conclusion

Platelet-Rich Fibrin (PRF) is increasingly used in dentistry for tissue regeneration and wound healing. Unlike earlier platelet concentrates, PRF uses an

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autologous approach without artificial additives or anticoagulants. Advanced forms like A-PRF and I-PRF, created with modified centrifugation techniques, offer enhanced growth factor release and improved tissue regeneration. However, histological evidence confirming whether these clinical gains represent true periodontal regeneration or simply connective tissue attachment is still lacking. Further research is needed to investigate the histological effects of PRF on intrabony and furcation defects in humans.

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