ISSN: 0976-3031

Available Online at http://www.recentscientific.com

CODEN: IJRSFP (USA)

International Journal of Recent Scientific Research
Vol. 9, Issue, 9(B), pp. 28753-28757, September, 2018

International Journal of Recent Scientific Research

DOI: 10.24327/IJRSR

Research Article

PLATELET RICH FIBRIN

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DOI: http://dx.doi.org/10.24327/ijrsr.2018.0909.2522

ARTICLE INFO

Article History:
Received 4th June, 2018
Received in revised form 25th May, 2018
Accepted 18th August, 2018
Published online 28th September, 2018

Key Words:
Autograft, Blood, Platelet poor plasma, Platelet rich fibrin**,** Wound healing,

ABSTRACT

Wound healing is a complex biological process which helps in repair or regeneration of damaged tissue. Platelet rich fibrin was introduced in 1990's. Platelet rich fibrin is a second-generation platelet concentrate widely used to accelerate soft and hard tissue healing and is a strictly autologous fibrin matrix containing a large quantity of platelet and leukocyte cytokines. Ross *et al*. were amongst the pioneers who first described growth factor from platelets. Choukroun's Platelet rich fibrin has been the latest development among the platelet concentrates. Growth Factors presentin platelet rich fibrin, Leucocyte activation platelet rich fibrin dwells among a new generation of platelet concentrate that jump-starts the healing process to maximize predictability. The major difference between platelet rich fibrin from platelet poor plasma which contains platelets, leukocytes, macrophages, neutrophils, lack of anticoagulant and presence of natural growth factors which enhance factor and more potent wound healing and regeneration. Newer advancement of platelet rich fibrin is advanced platelet rich fibrin which contains porous structure, more number of leukocytes leads to significantly enhance vascularisation. Apart from medicine, platelet rich fibrin is the most promising regenerative material in dentistry. This article we discuss about various uses of platelet rich fibrin in the field of dentistry.

INTRODUCTION

Excogitation in the concept of tissue engineering has brought about a drastic improvement in the healing response of tissues.[1]Focus has constantly been on devising a "wonder material" that is most effective in its regenerative potential. Various platelet-derived products or platelet concentrates have been introduced that act as biological mediators aiding the healing response. Platelet-rich fibrin (PRF) is one such product that has proved its worth and has edged past the others. The Choukroun's platelet rich fibrin has opened the flood-gates in the field of dentistry, majorly focusing on the improved healing and regeneration. Thus PRF has also be entagged as a healing biomaterial.[2]

The modern exploration of regenerative dentistry has added impetus onto the field of molecular biology. Assuming the present-day situation, it can be categorically documented as an archetype stint in the therapeutic armamentarium for dental disease. Regenerative endodontic procedures are defined as biologically based procedures designed to replace damaged structures, including dentin and root structures, as wellas cells of the pulp-dentin complex.[3]Using platelet concentrates is a way to accelerate and enhance the body's natural wound healing mechanisms[2].PRF is a second-generation platelet concentrate widely used to accelerate soft and hard tissue healing and is a strictly autologous fibrin matrix containing a large quantity of platelet and leukocyte cytokines.[4]

Ross *et al*. were amongst the pioneers who first described growth factor from platelets. Choukroun's PRF has been the latest development among the platelet concentrates. The relationship between pulpal and periodontal disease was first described by Simring and Goldberg in 1964.[5] The regenerative potential of platelets has been deliberated. The platelets release growth factors that are trapped inside the fibrin matrix following activation. These are considered to be the stimulant for mitogenic response in the periosteum and are responsible for bone repair during normal wound healing.[6] The superior understanding of physiologic properties of platelets in wound

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healing has led to their augmented therapeutic applications.[7] Nevertheless, there is still concern linked to the procedures for production of autologous fibrin adhesives.[8,9]Besides, legal restrictions on blood handling with concentrated platelet rich plasma have coexisted. In an effort too vercome these problems, it was contemplated to develop a new family of platelet concentrates, which came to be recognized as the platelet rich fibrin (PRF).[8]

Evolution

The healing of hard and soft tissue is mediated by a wide range of intra- and extracellular events that are regulated by signaling proteins. Although the knowledge about these molecules remains incomplete, platelets have been found to play a crucial role not only in hemostasis, but also in the wound healing process.[10]

Platelets are anucleate cytoplasmic fragments containing granules that are spherical or oval structures with diameters ranging from 200 to 500 nm. They form an intracellular storage pool of proteins vital to wound healing, including platelet-derived growth factor (PDGF), transforming growth factor (TGF), and insulin-like growth factor (IGF-I). Secretion of the active proteins follows the fusion of the granules with the platelet cell membrane, which subsequently bind to the transmembrane receptors of the target cells.[11] The first generation incorporates the platelet-rich plasma while the second generation involves the platelet-rich fibrin.

Platelets and Fibrin

Platelets are the second-most numerous corpuscles in the blood.[12] They are cytoplasmic fragments that lack core derived from megakaryocytes.[13,14] Their lifetime is between 7 and 10 days[14], and the normal peripheral blood concentration is 150-450 $\times 10^9$/L.[12] These unactivated platelets are biconvex discoid structures shaped like a lens with dimensions of approximately 2.0-4.0 by 0.5 μm and a mean volume of 7-11 fl.[12]

Platelet rich plasma (PRP) introduced for the first time by Marx *et al*. in 1998. The data reported by Marx suggested that PRP addition accelerated the rate and degree of bone formation.[15] PRP was developed to combine the fibrins sealant properties with growth factor effects of platelets, thus providing an ideal growth factor delivery system at the site of injury. These Growth factors exhibit chemotactic and mitogenic properties that promote and modulate cellular functions involved in tissue healing, regeneration, and cell proliferation.[16]

Clinical Applications[18,19]

1. Sinus lift procedures
2. Ridge augmentation.
3. Socket preservation technique.
4. Intrabony defects or osseous
5. Jaw reconstruction surgeries.
6. Soft tissue procedures like gingival grafts, subepithelial grafts.

Limitations[19]

1. Lack of uniformity in PRP preparation protocol as different platelet concentrations have different storage time.
2. Release of growth factors for a shorter period of time.
3. Antibodies to bovine factor Va may cross react with human factor Va and may produce coagulopathies and rare bleeding episodes.

Platelet-Rich Fibrin (PRF)

Concept and Evolution of PRF

A Second-Generation Platelet Derivative eveloped in France by Choukroun *et al*.in 2001. PRF is a second-generation platelet derivative because, unlike other platelet concentrates like PRP, this technique does not require anticoagulants nor bovine thrombin or any other gelifying agent. PRF is a strictly autologous fibrin matrix containing a large quantity of platelet and leukocyte cytokines.[4] PRF represents a novel measure in the therapeutic concept with elementary processing and absence of artificial biochemical modification like the use of bovine thrombin. The crux of PRF synthesis lies in the attempt to accumulate platelets and release cytokines in a fibrin clot.

The PRF clot is yielded by a natural polymerization process during centrifugation, and its natural fibrin architecture seems responsible for a slow release of growth factors and matrix glycoproteins during ≥7 days. Such a slow release is unimaginable to point out in most PRP techniques because of their brutal platelet activation, contiguous release of growth factors, and very light fibrin network produced to sustain the concentrate injection.[9]

Biologic Features

Growth Factors Presentin PRF, Leucocyte Activation PRF dwells among a new generation of platelet concentrate that jump-starts the healing process to maximize predictability.

It consists of the platelets, cytokines, and the fibrin matrix. Platelets and leukocyte cytokines play an important part in the biology of this biomaterial.[11] Degranulation of platelets leads to release of cytokines able to stimulate cell migration and proliferation within the fibrin matrix, launching the first stages of healing.[2,4] Fibrin matrix supporting the constitutes the determining element responsible for the real therapeutic potential of PRF. The biologic activity of the fibrin molecule highlights its significant cicatricial capacity.[2]

Functions and Role of Fibrin Matrix

Fibrin is an activated form of fibrinogen molecule present in plasma as well as the α-granules of platelets. It plays a significant role in platelet aggregation and achievement of hemostasis. The soluble fibrinogen is transformed into insoluble fibrin that polymerizes to a cicatricial matrix.(9). The slow and natural polymerization of fibrin results in its homogenous 3-dimensional organization during the centrifugation performed in PRF preparation. This leads to the intrinsic incorporation of platelet cytokines and glycan chains in the fibrin meshes .The fibrin matrix present in PRF is flexible, elastic, and very strong. It consists of weak thrombin concentrations which entails equilateral junctions.

These connected junctions permit the ecesis of a fine and flexible fibrin network capable of supporting cytokines and cellular migration that occurs. This results in an increase in the life span of these cytokines as their release and use will occur at the time of initial cicatricial matrix remodeling. Fibrin meshwork in PRF differs from that in PRP. In PRP, there are bilateral junctions resulting in a rigid network that does not

honor the cytokine enmeshment and cellular migration. The increased thrombin required for rapid setting of the PRP leads to a rigid polymerized material.[20]

Role of Fibrin in Angiogenesis

Entrapment of cytokines in the 3-dimensional architecture of fibrin matrix results in their sustained release which is monumental in initiation of angiogenesis.[21] The cytokines responsible for this action include the FGF,VEGF, angiopoietin, and PDGF within the fibrin gel. It is the rigidity of the fibrin matrix that is instrumental in the process of angiogenesis in response to FGF and VEGF stimulation.[22]Increased expression of $\alpha v\beta 3$ integrin in response to fibrin allows the binding of endothelial cells to fibrin itself, fibronectin, and vitronectin.[23]

Fibrin Assisted Immune Response

Increased expression of CD11c/CD18 receptor on endothelial cells by fibrin aids in enhanced adhesion to endothelial cells and fibrinogen, and transmigration of neutrophils.[24] Fibrin and fibronectin also modulate the wound colonization by the macrophages.

Effect of Fibrin on Mesenchymal Stem Cells

Fibrin matrix acts as a scaffold for the undifferentiated mesenchymal cells that facilitate the differentiation of these cells thus aiding in tissue regeneration.

Effect of Fibrin on Osseous Tissue

Direct interaction between fibrin and the osseous tissue lacks significant documentation. However, bone morphogenic proteins enmeshed in fibrin matrix have the ability to be released consistently highlighting the angiogenic, hemostatic, and osteoconductive properties. Fibrin is accredited as a support matrix for BMP. BMPs enmeshed in fibrin are progressively released and are able to induce bone. Consistent release of VEGF, FGF and PDGF helps in angeiogenesis. Hemostasis is achieved through the ability of fibrin clot to trap circulating stem cells, allowing vascular and tissue restoration .

Preparation

Preparation of PRF follows the protocol developed by Choukroun *et al*. in Nice, France.[25] The protocol for PRF preparation is very simple; however it has to be manufactured just prior to its application.

Requirements

1. table centrifuge,
2. 10-mL dry glass test tube (without anticoagulant),
3. blood collection armamentarium.

The main advantages in PRF preparation are the single stage centrifugation and absence of bovine thrombin. The blood obtained from the subject is placed into the test tube and centrifuged immediately for 10 minutes at 3000 rpm.[9] Others have used 2700 rpm for 12 minutes with similar findings.[26]
The steps involved are as follows:

1. blood specimen is collected or drawn from the patient,
2. the blood specimen is placed in the centrifuge and is allowed to spin immediately for the stipulated time,
3. Following this the blood sample settles into various layers.

The absence of any anticoagulant grants the activation of platelets to set off a coagulation cascade. Due to the absence of the anticoagulant, the blood coagulates immediately upon contact with the glass tube. Initially, fibrinogen occupies the upper part of the tube, only till the circulating thrombin transforms it into a fibrin network.[4]

The layers that are formed are as follows:

1. The lower fraction containing the RBCs,
2. The middle fraction containing the fibrin clot,
3. The upper fraction containing the straw-colored acellular plasma.

The upper portion of the test tube containing the acellular plasma is removed. The middle portion containing the fibrin clot is then removed and is scrapped off from the lower part containing the red blood cells. The natural and progressive polymerization results in a fibrin clot formation with substantial embedding of platelets and leukocyte growth factors into the fibrin matrix.[27]

PRF Membrane

The clot can be squeezed between two gauge pieces to obtain an inexpensive autologous fibrin membrane. The serum exudate expressed from the clot is rich in proteins such as vitronectin and fibronectin.[28] This exudate may be used to hydrate graft materials, rinse the surgical site, and store autologous graft.

The PRF Box is commercially available to prepare the PRF membrane. The PRF clot is placed on the grid in the PRF box and covered with compress or lid which squeezes out the fluid from the clot. The membranes formed using this method had constant thickness which remain hydrated for several hours and have recovered the serum exudate expressed from the fibrin clots.

Clinical Implications of PRF

Oral Applications

1. PRF and PRF membrane have been used in combination with bone grafts to hasten the healing in lateral sinus floor elevation procedures.
2. Protection and stabilization of graft materials during ridge augmentation procedures.
3. Socket preservation after tooth extraction or avulsion
4. Root coverage procedures.
5. Regenerative procedures in treatment of 3-walledosseous defect.
6. In the treatment of combined periodontic endodontic lesion.
7. Treatment of furcation defect.
8. PRF enhances palatal wound healing after free gingivalgraft.
9. Filling of cystic cavity.

Extraoral Clinical Applications

Use of PRF in periodontology and oral and maxillofacial surgery has been largely described.

1. PRF promotes dentinogenesis by stimulating cell proliferation and differentiation of Dental Pulp Cells
2. To augment Achilles tendon repair.
3. PRFM can provide significant long-term diminution of deep nasolabial folds.[29]
4. Application in facial plastic surgery [30,31]

1. Nasolabial folds,
2. Facial volumization,
3. Superficial rhytides,
4. Acne scars,
5. Rhinoplasty,
6. Facial esthetic lipostructure,
7. Autologous fat transfer,
8. Rhytidectomy,
9. Depressed scar,
10. Dermal augmentation.

1. Healing of severe nonhealing lower-extremity ulcers.[32]
2. Repair of articular cartilage defects.[33]

PRF membrane functionalized by incorporation alkaline phosphatase induces the mineralization of PRF. Thus, PRF can also be a suitable material for bone replacement.[34]

PRF is an adjunct to the natural healing process and has the following effects:

1. The fibrin clot acts as a support through its mechanical properties which involve the protection of graft materials and also acts as a biological connector between the bone particles,
2. In addition to this the fibrin network is engaged incellular migration, mainly for the endothelial cells necessary for the neoangiogenesis, vascularization, and survival of the graft,
3. the process of healing is carried along and aided by the persistent release of various growth factors that include PDGF, TGF-β and IGF-1,
4. The presence of leukocytes and various cytokines enables the self-regulation of the infectious and inflammatory processes.

Advantages of PRF

a. No use of anticoagulants
b. Slow natural polymerization
c. 3D fibrin network forming a matrix aiding in cytokine retention for extended periods
d. Formulation of a PRF membrane that possesses elasticity and flexibility
e. Simple and cost effective

Limitations of PRF

1. Owing to the fact that PRF is an autologous product, the availability of this biomaterial in larger amounts is a concern. Hence, its usage in surgical procedures should be well supervised.
2. PRF possesses the circulating immune cells and antigenic molecules that prevent its use as an allogenic material. Also, there is an increased risk of transmitting infectious agents.

CONCLUSION

The application of autologous platelet-rich fibrin could present new possibilities for enhanced healing and functional recovery. However, the effectiveness of PRF in regenerative procedures should be evaluated in studies that involve a large number of subjects. Moreover, the use of PRF in randomized control trials has to be encouraged.

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How to cite this article:

Navarasu M *et al*.2018, Platelet Rich Fibrin. *Int J Recent Sci Res.* 9(9), pp. 28753-28757.
DOI: http://dx.doi.org/10.24327/ijrsr.2018.0909.2522

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