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Role of Platelet Concentrates in Periodontal Regeneration- An Overview

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***Abstract*: Platelet plays an important role in hemostasis and wound healing; platelet growth factors are well known for healing cytokines. Platelet concentrate is derived from the patient's own blood, this technique uses a centrifuge to separate out the patient's own blood components by their densities, RBC are denser that will move to the bottom, plasma fraction is least dense will float on the top layer, the (buffy coat) which contain majority of platelet will be sandwiched between the plasma and above RBC. Platelet Rich Plasma (PRP) and Platelet Rich Fibrin (PRF) are extensively used analogue platelet concentrate in periodontal regeneration. PRF has better efficiency when compare to PRP. This rationale has been attributed to the difference in structure of fibrin matrix. The Concentrated Growth Factor (CGF) is an excellent and a novel regenerative tool in the field of periodontics and regenerative dentistry. It is adopted without the use of chemical which is more ecofriendly. It consists of numerous growth factors which enhance its action and promotes wound healing. It is used along with the autologous bone particle to induce bone regeneration. It has the ability to regenerates both soft and hard tissues. It is effective, economical, bio compactible, resorbable biomaterial.**

***Keywords*: Autologous Biomaterial, bone regeneration, concentrated growth factor, plasma, regenerative dentistry, stem cell therapy.**

1. Introduction

Periodontal repair and regeneration is the ultimate goal in the treatment of periodontal defects by promoting effective wound healing. Various regenerative techniques including root surface bio-modification, guided tissue regeneration, guided bone regeneration and application of growth factor were used to achieve regeneration [1]. Various biomaterials such as natural and synthetic have been tried for many years to improve wound healing of soft and hard tissues. Naturally occurring material known as "Autologous Biomaterial" are present in the body and they help in repair regeneration and healing similarly synthetically generated alloplastic materials have also shown good result in many fields of regenerative dentistry, but the drawback is that it may exhibit foreign body reaction [2, 3]. Platelets participate in both the innate and adaptive intravascular immune responses. The platelet cell membrane has receptor for collagen. Structurally the platelet can be divided into four zones namely peripheral, sol-gel, organelle and membranous zone Platelet concentrates (PCs) is biological autologous products derived from the patient's whole blood and consist mainly of concentration of platelet and growth factors (GFs) Concentrated Growth Factor (CGF) was first developed by Sacco in 2006 as a new technology in regenerative medicine. CGF is an advanced second regenerative platelet concentrated obtained by different centrifugal methods. CGF is fibrin rich organic matrix which contains growth factor, platelets, leukocytes and CD34+ stem cell which help in regeneration process [4]. CGF is different from Platelet Rich Plasma (PRP) and Platelet Rich Fibrin (PRF) in the method for production because no additives are added during production. CGF has higher adhesive strength, tensile strength, higher viscosity when compared to other platelet preparation [5]. CGF is a biological inducing material which improves the quality of the formed bone and help in facilitating the formation of bone and healing tissues [6]. Description of platelet concentrates has been illustrated in Figure 1.

2. Classification

Schematic representative diagram illustrating the classification of platelet concentrates has been depicted in Figure 2.

A. Platelet rich plasma (PRP)

Platelet rich plasma is the first generation of platelet concentrate which showed positive results. It is a high concentration of platelet suspended in a small volume of plasma. Platelet rich plasma is also known as platelet rich growth factor (PRGF). The concept and description of PRP started in the field of hematology [9]. They created the term PRP to describe the plasma with platelet count above that of peripheral. It is used as transfusion product to treat patient with thrombocytopenia, bone morphgenic protein, a subtype of TGF has been shown to induce formation of a new bone at the implant site with bone substitute particle. PRP act as a stimulation of normal healing. PRP blood clot consist of 4% RBC, 95% platelets, 1% WBC [10, 11]. The components of PRP are:

1. Growth factor
2. WBC and phagocytic cell

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3. Native fibrinogen concentration
4. Vasoactive and chemoactive agents
5. High concentration of platelets

1) P-PRP Pure platelet rich plasma

Pure platelet rich plasma such as PRGF (endoret technique) is prepared without the leucocytes and with low density fibrin network. It is proposed that all the product of this family can be used as liquid solution or activated gel form. So, it can be injected or placed during gelling on a skin wound. Many methods of preparation exists, one common method is cell separators (continuous flow of plasmaphoresis) [12]. One large advertised method of P-PRP is known as PRGF (Plasma Rich in Growth Factor or Preparation Rich in Growth Factor) Endoret technique is used mainly in sport medicine. Significant concern of this technique is lack of ergonomics and need for approximate pipetting steps during the preparation [13]

2) L-PRP Leukocyte platelet rich plasma:

L-PRP products are preparations with leukocytes and with a new density fibrin network after activation. As per definition like P-PRP all the products of this family can be used as liquid solution or activated gel form, so it is injected in sports medicine. Particularly many automated protocols are used, they are harvest smart - pre P (Harvest Technologies , Plymouth , MA, USA) and Biomet GPS III (Biomet Inc., Warsaw USA).Other kits also exist such as plateletex , cprague , (Zech republic) or Regan PRP [14].

B. Platelet rich fibrin (PRF)

Platelets rich fibrin was first developed in France for use in the field of oral and maxillofacial surgery. Choukroun's platelet-rich fibrin (PRF), a generation in platelet concentrate is a leukocyte and platelet rich fibrin biomaterial with a specific composition and three-dimensional architecture where autologous platelets and leukocytes are present in a complex fibrin matrix to accelerate the healing of soft and hard tissue [15]. It is a quite modern platelet concentrate. It is achieved by simple preparation with no biochemical manipulation of blood. It does not require anticoagulants or bovine thrombin. It is easily used with low rate of mistake during preparation. It is able to stimulate osteogenesis in bone environment in addition to angiogenesis. PRF clot concentrates 97% of platelets and >50% of leukocytes in a specific three dimensional distribution. It consists of cytokines, glyconic chain and structural glycoprotein in-meshed with slowly polymerized fibrin network [16]. They are classified into two types namely: i) P-PRF (poor platelet rich fibrin) and ii) L-PRF (Leucocytes and platelet rich fibrin).

1) P-PRF (Poor platelet rich fibrin)

These are prepared without leucocytes and with low density fibrin network and only exists in a strongly activated gel form, so, cannot be injected or used like fibrin glues. It can be used only as fibrin membranes or solid materials [17]. There is only one product in the family commercially known as fibrinet PRFM (platelet rich fibrin matrix). The main inconvenience in this technique is cost and relative complexity in comparison to the other forms of PRF , the LPRF leucocyte platelet rich fibrin [18].

2) L-PRF (leucocytes and platelet rich fibrin)

These preparations are with leukocytes and with a high density fibrin network and exist in a strongly activated gel form and cannot be injected. They can be handled like a real solid material for any application. This technique is developed and evaluated as an open access technique based on one step centrifugation of blood without anticoagulant and blood activator [19].

3) Preparation of PRP/PRF

PRP is prepared by a process known as differential centrifugation. It is made from autologous blood and is used to deliver growth factor in high concentration to the site of bone defect. It is prepared by 2 techniques [20, 21]:

1. General- purpose cell separator
2. Platelet - concentrating cell separator

It is classified into 3 basic components

1. Platelet poor plasma
2. Platelet rich plasma called as buffy coat
3. Dense red blood cells

Preparation protocol was first developed by Choukrount et al. in mice. The protocol is very simple. It tries to accumulate platelets and the released cytokines in fibrin clot. For preparation PRF needs only centrifuged blood without any addition of anti-coagulant and bovine thrombin [22]. The blood collected from subject is placed into the test tube and centrifuged immediately for 10 minutes at 3000rpm. Other has used 2700 rpm for 12 minute with similar findings [23, 24]. The resultant product consists of three layers. Top most layers consist of acellular plasma, PRF clot in the middle and a red capsule base at the bottom. The natural and progressive polymerization results in a fibrin clot formation with sub embedding of platelets and leukocyte growth factors into the fibrin matrix [25].

4) 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 protein such as vitronectin and fibronectin. It is used to hydrate graft materials store autologous graft. PRF box is available to prepare PRF membrane. PRF clot is placed in the box and compressed. The membranes formed using this method has uniform thickness and remain hydrated for several hours [26, 27].

C. Advanced second generation- CGF (concentrates growth factor) preparation

CGF is autologous preparation taken from the venous blood collected in sterile tubes without anticoagulant solution. The tubes are kept for centrifugation with one step centrifugation protocol for about 30seconds acceleration followed by 2min-2700rpm,4min-2400rpm,4min-2700rpm,3min- 300rpm , 36 seconds as a deceleration and stop [28].

Results in four phases [28, 29]:

1. Superior phase – serum
2. Interim phase - fibrin buffy coat
3. Liquid phase - growth factor
4. Lower phase - red blood cells

1) Superior phase (serum)

Superior phase is represented by serum. It is a clear straw colored fluid which is lightest and most liquid part of blood. It is fibrinogen free and has only few cells. It consists of 92.5% water, 7% protein, mineral salts, CO2, albumin, antibodies, glycosides, amino acid, lipids ,enzymes, hormones and inorganic electrolytes.

2) Interim phase (fibrin buffy coat)

Fibrin block consists of three - dimensional polymer network with inter fibers all collected in a single phase in the form of gel, when viewed under electron microscope this layer is constituted by thick and thin elements. During polymerization reaction the diameter of fibers grows till the end of reaction. Many corpusculated components are combined which determine numerous actions, include

A. Plasma and platelet cytokines: repair, anti-inflammatory; phagocytic or lytic effect during repair (TNF-A)
B. Platelet: Transmission of the signals and release the GFS

The fibrin gel blocks have excellent resistance for cavity filler and gives, membrane support. Factor XIII is activated by thrombin stabilizes the fibrin clots and provides protection from plasma degradation, resulting in higher fibrin tensile stress ability and prolong the duration of growth factor activity. It enhances the process of cell proliferation and osteogenesis differentiation.

3) Liquid phase (Growth Factor)

The growth and uni-potent stem cells are located just below the buffy coat and above the dense coat portion. The liquid phase is mixed with autologous bone graft to get high performance activated graft.

4) Lower phase (Red Blood Cell)

The lower phase is dark reddish dense gel. It consists of high concentration of RBC and also few white cells, clotting factors and platelets. It is used in pure form or mixed with bone graft cavities.

3. Mechanism of Action

CGF releases various growth factors such as Platelet-derived growth factor (PDGF), Transforming growth factor-β1 (TGFβ1) and β2 (TGF-β2), Fibroblast growth factor (FGF), Vascular endothelial growth factor (VEGF), Brain derived growth factor (BDGF) and Insulin-like growth factor (IGF) which stimulate cell proliferation, matrix remodeling and angiogenesis [30]. In vitro study have proved that growth factors like TNF-α and BDGF showed fast kinetic release from the concentrate and reached its maximum accumulation in 1st and 3rd day respectively [31]. Similarly PDGF-AB, TGF- β1 and IGF-I had constant kinetic release and reached its maximum in 3rd and 6th day respectively. VEGF and BMP-2 had slow kinetic release and reached its maximum in 8th day. These growth factors predominantly play a role in osteoblast proliferation and differentiation [32].

CGF acts by degranulation of the alpha granules in platelets that contain growth factors which play a vital role in early wound healing [33]. The biphasic platelets in CGF is accelerated by thrombin, induce the release of growth factors and other substances which enhance the wound-healing process by increasing cellular proliferation, matrix formation, osteoid production, connective tissue healing, angiogenesis and collagen synthesis [34].

A. Clinical applications of PRP [35]

1) Periodontal defect treatment
2) Root coverage procedure
3) Ridge augmentation.
4) Guided bone regeneration
5) Sinus lift grafting and implant surgery
6) Mandibular and maxillary reconstruction (tumor and trauma related defects)
7) Dermal fat graft and orthopedic surgery

B. Clinical applications of PRF [36]

1) In intra bony defect
2) For root coverage procedure
3) In periapical lesion
4) In treatment of furcation defects, socket preservation.

C. Clinical applications of CGF [37]

1) Reconstruction of soft tissue and bone defects
2) In patients undergoing cosmetic surgery like facelifts, neck lifts, cardiovascular surgeries, oral and maxillofacial surgeries
3) CGF is used to fill extraction sockets, fill the cavity after cystectomy, sinus lift procedure, ridge augmentation surgeries, recession coverage and also mixed with autologous bone particles or biomaterials to fill the bone defect.

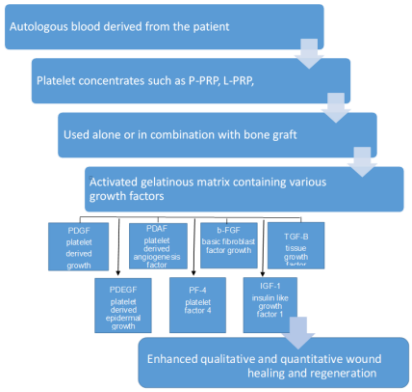

Fig. 1. Description of platelet concentrates

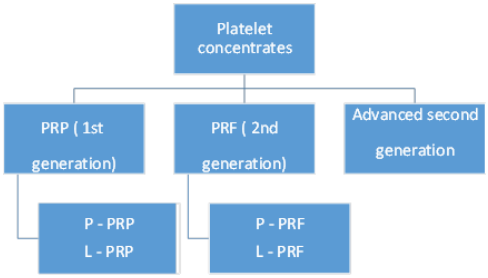

Fig. 2. Schematic Representative Diagram showing the Classification of platelet concentrates

D. Advantages of PRF [39]

1) It helps in restoration of bone defect crafting minor cysts or by extraction of teeth
2) PRF is quick and conveniently produced
3) It can be used solely or in the combination of other bone graft
4) Accelerates the healing rate of graft bone
5) It circumvents the addition of external thrombin as polymerization is completely natural processes refraining from any risk of immunological reaction.

E. Disadvantages of PRF [40]

1) Being autologous in nature the find amount is very less
2) It becomes very difficult PRF after preparation and it shrinks
3) Clot polymerization requires clinical experience
4) Patient with bleeding disorder or hematologic
5) Experienced surgeon /physician are required to determine if PRF is adequate and effective.

Table 1
Table showing the advantages and disadvantages of PRP

Advantages of PRP	**Disadvantages of PRP**
Soft autologous preparation free from concern over transmissible disease such as HIV, Hepatitis, etc.	Concern over the use of bovine thrombin the fact that bovine thrombin has been associated with Development of antibodies to clotting factor V, IX thrombin which had occasionally lead to life threatening Coagulopathies.
Convenient for patient. Blood is collected in the immediate Preoperative period.	Lack of uniformity in PRP preparation protocol as different platelet concentration has different storage time.
Presence of platelet brings cytokines and growth factors to the site of the surgery which helps in rapid regeneration a manner that would not occur with fibrin glue [38].	

4. Conclusion

Platelet concentrates has been used in various application of dentistry since many years. Technological advancement in this field shows promising result in use of Platelet Rich Fibrin (PRF) in periodontal regeneration. Various studies have been conducted to determine the utilization of PRF in various procedures in the fields of periodontology, oral surgery, and implant dentistry and encouraging results obtained in both soft and hard tissue regeneration. Various factors like speed, duration of centrifuge, temperature and blood hematocrit influences the quality of fibrin scaffold. The prominent role of leukocytes or fibrin in PRF scaffolds could be a potential avenue for future research.

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