Application of Platelet Rich Plasma and Platelet Rich Fibrin in Dentistry

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ABSTRACT

Advancement in medicine demands less invasive therapies and faster recovery time. A recent innovation in dentistry is the preparation and use of platelet concentrates, which contain concentrated suspension of the growth factors. These help in wound healing and tissue regeneration. Application of Platelet -rich plasma (PRP) and Platelet rich Fibrin (PRF) are new approaches in tissue regeneration and a developing area for clinicians and researchers. The aim of this review is to discuss the efficacy of PRP and PRF in various fields of dentistry.

Keywords: Platelet Concentrates, Platelet Rich Plasma, Platelet Rich Fibrin, Tissue Regeneration, Growth Factors, Dentistry.

INTRODUCTION

The complex process of healing or tissue repair involve cellular organization, chemical signaling, and the extra-cellular matrix. The tissue hemostasis and wound healing are carried out by platelets. Various growth factors which stimulate cellular proliferation, healing, growth and cellular differentiation are released on activation of the platelets. Various bioactive surgical additives are developed to regulate the inflammation and increase the speed of healing process.[1] Enhancement of the regenerative process of human body by utilizing the patient's own blood is a unique concept to dentistry.

BLOOD PHYSIOLOGY

Blood consists of liquid plasma, formed elements (cells) which mainly comprises of erythrocytes, leukocytes and thrombocytes. Approximately one thousand billion blood cells are produced daily. Blood plasma contains about 90-92% water, 6-8% protein, prothrombin, thrombin, factor-III to XIII and Complement system.[2] Platelets are 2.5µm long cell fragments, developed from bone marrow cells called megakaryocytes and regulated by thrombopoietin. The total count of platelet is 150,000 to 450000 platelet/µL. They lack nuclei and they contain mitochondria, microtubules, α granules, dense granules and lysosomes. Alpha granules are most abundant in platelets and they contain adhesive proteins. These adhesive proteins upon activation secretes coagulant and fibrinolytic proteins such as Factor V, IX, XIII, Antithrombin and Plasminogen.[3] Increased leukocytes in PRP and increased pro inflammatory cytokines and reactive oxygen species which inhibit healing process, so leukocytes count has to be controlled. RBC rich PRP causes synovial cell death and deleterious effect in cartilage regenration, so RBC count also should be controlled.

PLATELET ULTRASTRUCTURE has 4 ZONES

Peripheral zone contains Plasma memebrane rich in Glycocalyx (Glycoprotein), Lipid bilayer area and Actin filaments.

Sol gel zone contains Actin microfilaments.

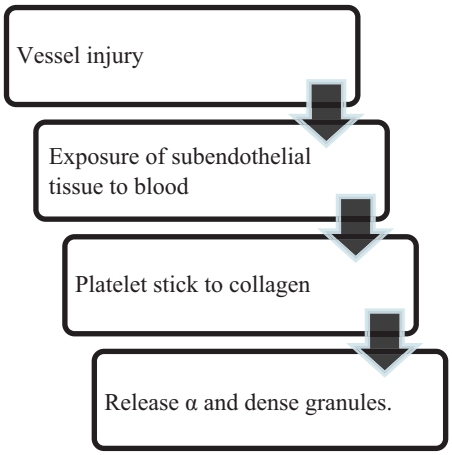
Organelle zone contains α and Dense granules, Lysosomes.

Membrane system contains Endoplasmic reticulum, Golgi Apparatus and Plasma Membrane.

PLATELET FUNCTION

The major function of platelet is to enhance Hemostasis through 4 steps**(Flow chart-1)** namely,

- Adhesion
- Activation
- Secretion
- Aggregation



Flow chart-1: Steps in hemostasis

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HISTORY OF PLATELET CONCENTRATES

Platelet regenerative abilities was first described in 1974. Its clinical applications began in the field of medicine in 1987 in an open heart surgery by M.Ferrari. In 1990, Gibble and Ness developed Fibrin gel biomaterial which acts as hemostatic agent and has adhesive properties. In 1997, Whitman et al first introduced PRP. It was later developed by Dohan et al in 2001.Whitman and colleagues called PRP as autologous alternative to Fibrin glue. The main difference between these two are, PRP contains increased platelet and native concentration of Fibrinogen. French Oral Maxillofacial Surgeon Joseph Choukroun et al in 2001 created 2nd generation platelet concentrate PRF.[4]

DEFINITIONS

PLATELET CONCENTRATES

Biological autologous products derived from patient's whole blood that consists mainly of supra physiological concentrations of platelets and growth factors.

PLATELET RICH PLASMA (PRP) - First generation

PRP is a product derived from the blood, numerous substances are released from PRP, that promote tissue repair. It also affect the behaviour of other cells mainly by modulating the inflammation and formation of new blood vessels.[5]

PLATELET RICH FIBRIN (PRF) - Second generation PRP

Presence of autologous platelets and leukocytes in the complex fibrin matrix, which accelerate the healing of soft and hard tissue. It is also used in tissue engineering

CLASSIFICATION OF PLATELET CONCENTRATES

- **Platelet concentrates**
  - ► Platelet rich plasma (PRP)
  - ► Platelet rich fibrin.(PRF)
- **Pure form (leukocyte poor)**
  - ► P-PRP, P-PRF
- **Rich in leukocytes**
  - ► L-PRP, L-PRF **(Figure-1).**
- **Other forms**
  - ► **Advanced PRF** or Choukroun's PRF- A-PRF **(Figure-1).**
  - ► **Injectable PRF (I-PRF) is obtained by** reducing the centrifuge speed and leukocyte infiltration into the red blood cell fraction is minimized.
  - ► **Concentrated Growth Factors (CGF)** developed by Rodella et al in 2011.It is larger, denser and richer in growth factors compared to PRF.
  - ► **Titanium PRF (T-PRF)-** Titanium more effective in platelet activation than silica used in glass tubes. It has highly organised fibrin network compared to L-PRF[6] **(Figure-2).**

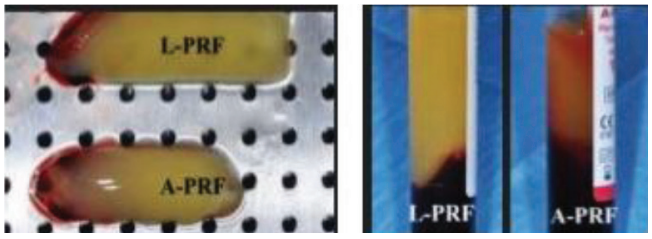


Figure-1: Types of PRF

AVAILABLE FORMS OF PLATELET CONCENTRATES

P-PRF, L-PRF are available in strong gel form and as solid material.

P-PRP, L-PRP are available in liquid or gel solution.

GROWTH FACTORS

Growth factors are major component of platelet concentrates, the main growth factors are as follows.

- PDGF-Platelet Derived Growth Factors
- PDGF-AA, PDGF-BB, PDGF-AB.
- TGF-β- Transforming Growth Factor Beta
- TGF-A1, TGF-A2
- IGF- Insulin Growth Factor
- EGF-Epidermal Growth Factor
- VEGF- Vascular Endothelial Growth Factor
- PDAF- Platelet Derived Angiogenesis Factor
- PF-4- Platelet Factor 4
- Rh PDGF- Recombinant Human Growth Factors

ADHESIVE PROTEINS

Platelet concentrates also contain adhesive proteins, which are as follows.

- Adhesive proteins are Vitronectin, Fibrin and Fibronectin
- PRP contains adhesive proteins which helps in
  1. Osteoconduction
  2. Matrix for bone and connective tissue
  3. Epithelial migration.

WOUND HEALING (FIGURE-3)

The platelets play a critical role in primary hemostasis and thrombosis. They also act as relevant modulators of other physiopathological processes including inflammation and tissue regeneration. These processes are mediated through the release of growth factors and extracellular

Figure-2: Titanium test tube for T-PRF preparation
Courtesy**:** Dr.Abdelrhman, Platelet rich fibrin in dentistry., slideshare.net

matrix modulators that promote (i) revascularization of damaged tissue (ii) restoration of damaged connective tissue (iii) proliferation and differentiation of mesenchymal stem cells into tissue-specific cell types. Thus platelet-rich plasma (PRP) derivatives are used in regenerative medicine[7] (Flow chart-2). There are four phases of Tissue Healing.

- Hemostasis
- Inflammatory
- Reparative
- Remodelling

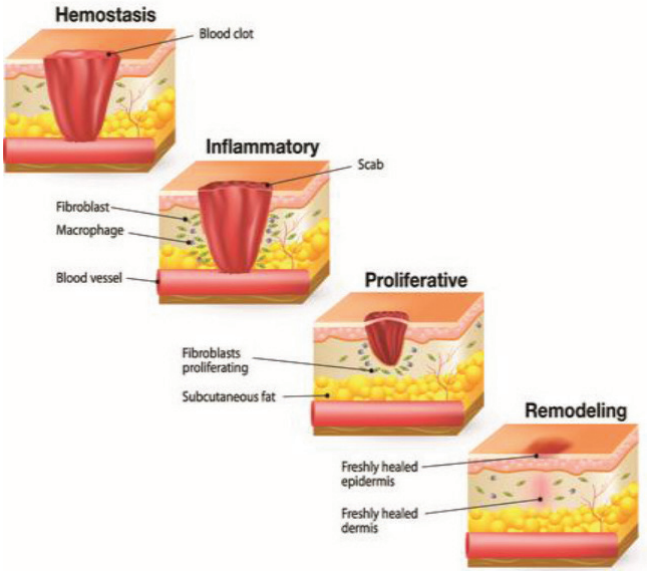
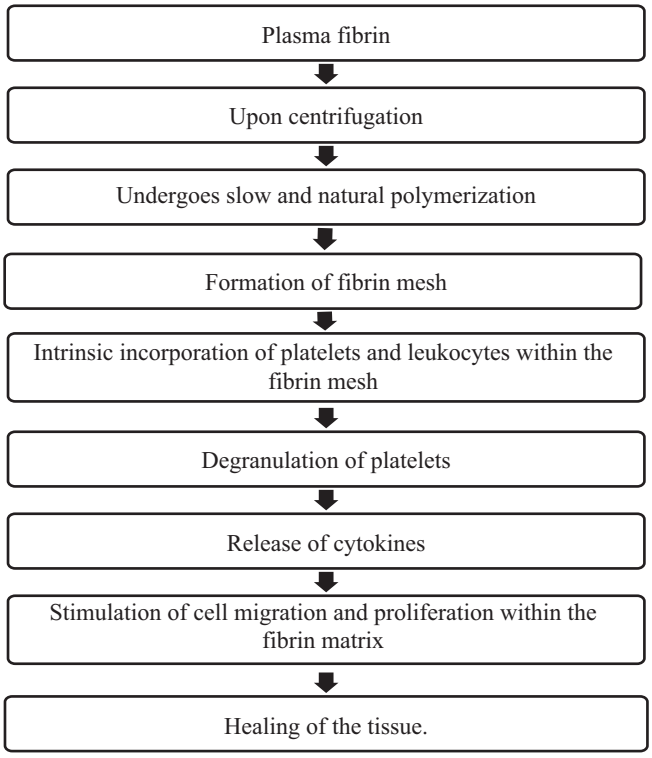


Figure-3: Wound healing
Courtesy: How Wounds Heal: The 4 Main Phases of Wound Healing., Shieldhealthcare.com



Flow chart-2: PRF usage in wound healing

HEMOSTASIS PHASE

- In this phase, blood clot formation leads to matrix formation and allow cell movement and proliferation.

INFLAMMATORY PHASE

- This phase occurs at 1st to 7th day after Injury. Platelet release GF that attract inflammatory cells like Neutrophils, monocytes and lymphocytes to the injury site. These inflammatory cells secrete pro inflammatory cytokines- TNF α, IL-1,6,8. They help in Angiogenesis and tissue healing.

REPARATIVE PHASE

- In this phase, mesenchymal stem cells (MSC) are recruited from adjacent soft tissue or blood vessels. BMP & TGF β helps in bone regeneration by inducing osteoblast differentiation.

REMODELLING PHASE

- In this phase, there occurs replacement of woven bone with lamellar bone.

PLATELET RICH PLASMA

- It is 1st generation of platelet concentrate, prepared using centrifugation or plasmapheresis. It can be stored in room temperature. Centrifugation involves one or two steps using various forces(g) and centrifugation times (CT).Centrifugation time ranges from 8 to 30 min. Force (g) ranges from 100-1000g.[8]

PREPARATION

ONE STEP CENTRIFUGATION

Plasma rich in Growth Factors (ANITUA'S PRGF).Plasma is divided into two parts here as follows,
Top fraction (Platelet poor plasma) and bottom fraction including Buffy coat contain increased concentration of platelet.

TWO STEP CENTRIFUGATION

Total time of the procedure is 12minutes. 450ml of blood bag containing citrate phosphate dextrose anticoagulant. 1st spin separate blood in the centrifugation tube into 3 layers (5600 rpm-Hard spin). RBC in bottom. Buffy coat rich in platelet and leukocytes in the middle.
Platelet poor plasma (PPP) in top.

P-PRP PREPARATION (FIGURE-4)

PPP layer, upper part of buffy coat layer transferred to another tube and second centrifugation (2400rpm-soft spin). PPP layer is removed, platelet pellet cone in bottom of the centrifugation tube is resuspended in small volume of plasma to produce P-PRP. In 30 ml of plasma, about 5lakh to 1 million platelet can be obtained.

L-PRP PREPARATION

PPP Layer, whole Buffy coat and part of RBC layer are transferred to another tube and second centrifugation takes place. L-PRP obtained is applied without activation to site, because collagen or thrombin at the site of injury activates

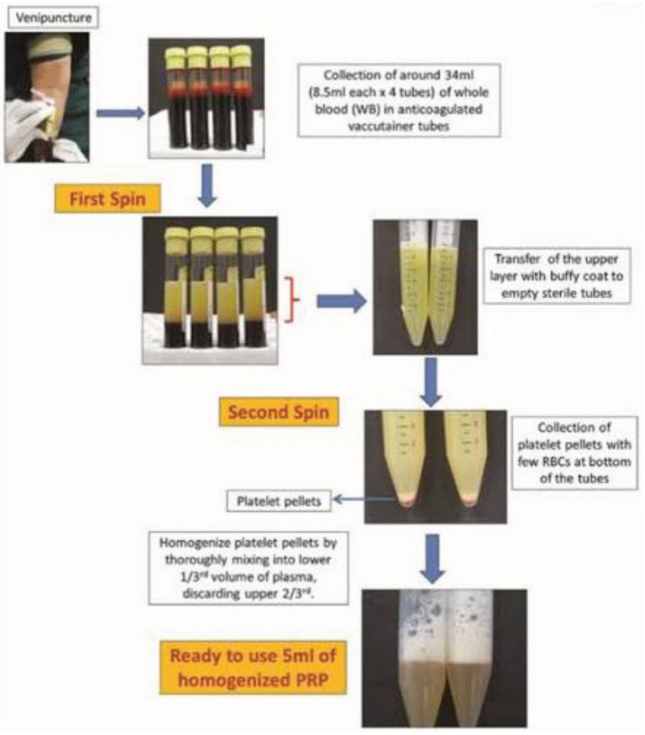


Figure-4: PRP preparation
Courtesy: Dr. Shraddha Kode, Platelet rich fibrin-Role in Periodontics., slideshare.net

platelets. ACTIVATORS used are 10,000 units of Bovine thrombin in powder form and 10ml of 10% CaCl2 mixture. 7ml of PRP and 2ml of air drawn into 10ml syringe. 1ml of above activator mixture is added to syringe. In 5-30 seconds-fibrin gel is formed, as citrate is neutralized and thrombin activates polymerization of fibrin and degranulation of platelets.[9]

BIOLOGICAL PROPERTIES OF PRP

- Allogenic PRP (aPRP, homologous) can be used in patients who refuse to venipuncture and blood drawing procedures. Decreased concentration of PRP doesn't enhance wound healing. Increased concentration has no further enhancement of wound healing.
- Based on production of GF: It is critical in regulation and stimulation of healing process. It regulates the cellular process, mitogenesis, chemotaxis, differentiation and metabolism.[10]

MECHANISM OF ACTION OF PRP

- Growth factors are released within 10 minutes after clotting. 95%- pre synthesized growth factors are secreted within 1 hour. Additional growth factors are secreted for 7 days of total life span of platelet. Interaction between GF and surface receptors on target cells- Activates intracellular signalling pathway leading to production of proteins need for regeneration (cellular proliferation, matrix formation, osteoid production and collagen synthesis).

ADVANTAGES AND BENEFITS OF PRP

- It is obtained from by-product of the patient's own blood; therefore chances of infectious disease transmission is rare. As there is super saturation of the wound with PRP, growth factors fasten tissue regeneration. Can be easily generated in the dental office while patient is undergoing out patient surgical procedure, like placement of dental implants, extraction defects, variety of grafting and soft tissue procedures. Since PRP is harvested with 8-10ml of blood, patient need not bear the expense of the harvesting procedure in hospital or blood bank. Preparation time is relatively short and concentrate can be obtained within 12 min.[11]

RISK OF PRP USAGE

- As gel formation after isolation of PRP involve use of bovine thrombin, which may be associated with antibodies to factors V, IX and thrombin, resulting in life threatening coagulopathies. Bovine thrombin preparations has factor V, which can stimulate immune system if challenged by a foreign protein. Safer options include use of recombinant human thrombin or autologous thrombin.
- **Contraindications** - Patients with Platelet dysfunction syndrome, septicemia, anemia (Hb<10g/dl), critical thrombocytopenia, hemodynamically unstable patients and pregnancy. Therefore, the sequence of procedures, healing periods and possible risk and complications should be clearly explained to patients prior to treatment.

PLATELET RICH FIBRIN

- It is Second generation of platelet concentrate. There is increased L-PRF usage than P-PRF. PRF is prepared without use of anticoagulant or bovine thrombin. The procedure require centrifuge table, blood collection kit, collecting tube 10ml.Time lapse is important for success of PRF.[12]

L-PRF PREPARATION (FIGURE-5)

- Single spin protocol (3000rpm-10min). Centrifuge cause the blood to contact the test tube wall, which activates platelet and coagulation cascade. Slow polymerization during PRF preparation generates fibrin network. This enhance cell migration and proliferation. L-PRF gel form can be directly applied to the site.[13]

P-PRF PREPARATION (FIGURE-5)

- 2 spin protocol: Blood collected in tube (Tri sodium citrate & A separator gel). Centrifuged at 1100rpm

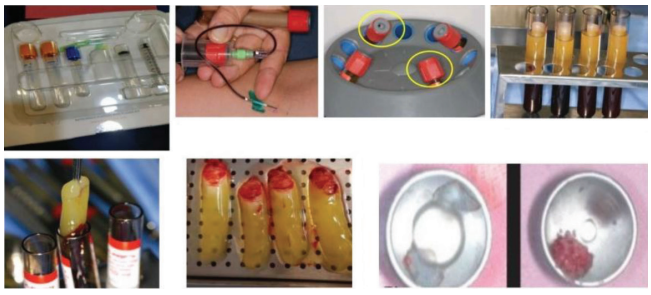


Figure-5: PRF preparation

for 6 min. Separates blood into 3 layers- RBC, Buffy coat, PPP. Buffer coat and PPP layers are activated with CaCl2. Second centrifugation at 4500rpm for 15 minutes. PRFM(Matrix) clot formed is applied to the site.[14]

ADVANTAGES OF PRF

- Ease of preparation and application. The procedure is simplified and cost effective process. It supports cytokines enmeshment and cellular migration.[15]

DISADVANTAGES OF PRF

- The quantity of PRF obtained is low. Its clinical benefit depends on time interval between speed of handling between blood collection and centrifugation. It contains circulating immune cells-so totally specific to the donor.[16] It is should be used immediately because it results in shrinkage altering structural integrity and biological properties. It is stored in refrigerator, therefore there is risk of bacterial contamination.

ADVANTAGES OF PRF OVER PRP

- PRF minimized autologous blood manipulation including easier preparation. Entire process is natural, without any external manipulation leading to the absence of any immunological reaction. No use of bovine thrombin and anticoagulants. It doesn't require a chemical manipulation of the blood, which makes it strictly an autologous leukocyte –platelet rich fibrin matrix.[17] This matrix acts as a biodegradable scaffold that favours the development of microvascularization and guide epithelial cell proliferation and migration to its surface. It is used as a membrane, it avoids a donor site surgical procedure and results in reduction in patient discomfort during the early wound healing process. It can be used in combination with bone grafts or as one layer, depending on the manipulation. It is more efficient in cell migration and proliferation. Compared to PRP, its more efficient and show better clinical results.[18]

CLINICAL APPLICATIONS OF PLATELET CONCENTRATES

SINUS AUGMENTATION

Sinus augmentation is a surgical procedure aims to restore the resorbed bone in the posterior maxilla caused by tooth loss. Sinus augmentation with autogenous bone grafts by the lateral window technique was reported by Boyne and James in the 1980s and developed by Tatum. PRF mixed bone substitute or PRF has so far solely been used as a graft material for sinus augmentation using both the lateral and crestal approaches.[19] The addition of PRP to anorganic bovine bone (ABB) increased the volume of newly formed bone and improved the osteoconductive properties of ABB, although it did not affect the implant success compared to ABB alone.[20] Only limited randomized controlled clinical trials evaluate the use of PRF in sinus floor elevation as a sole filling material or with bone substitutes. Further studies are needed to validate this treatment strategies.

ALVEOLAR RIDGE AUGMENTATION

Different augmentation techniques such as ridge augmentation, guided bone regeneration (GBR), and ridge splitting and expansion can be used to manage alveolar ridge resorption. In alveolar ridge augmentation with the titanium mesh (Ti-mesh), it was found that covering the mesh with PRP prevents the mesh exposure and bone resorption. PRP was found to significantly increase alveolar ridge width and the percentage of vital bone achieved with cancellous allograft.[21] In addition, covering the autogenous bone blocks in anterior maxillary augmentation with PRF increased bone width and decreased bone resorption.

PERIODONTAL SURGERY

Regenerative periodontal procedures induce regeneration at the alveolar bone and cementum and develop a new functional periodontal ligament.[22] PCs can be used alone or as an adjunctive material for treating intra-bony periodontal defects. PRP or PRF can reduce pocket depth and improve clinical attachment level. There is no beneficial effect found when it is used along with guided tissue regeneration (GTR).

SOCKET PRESERVATION

Platelet concentrates are being used in socket preservation procedures. It enhances healing and promote regeneration. The usage of L-PRF reduced the healing time and bone resorption in these cases. PCs reduce alveolar osteitis.[23] However, there are only few evidences available to support the use of PCs in socket preservation.

IMPLANT SURGERY

Platelet concentrates have been used prior to implant placement and in treating bone defects. There is moderate evidence available to support the use of PCs in the early phases of osseointegration. Both PRF and PRP have been found to reduce marginal bone loss around dental implants. The application of PRF during immediate implantation does not seem to have any significant role in healing or maintaining implant stability.[24]

ENDODONTIC SURGERY

PCs have been used in different root canal procedures including apexification, apexogenesis, pulpotomy, and endodontic apical surgery. PCs have been found to enhance peri apical bone regeneration, root development, and pulp vitality.[25]

MANAGEMENT OF PERIAPICAL PATHOLOGIES

Jaw cysts are pathological defects formed within the jaw bones or soft tissues. Radicular cysts are the most common inflammatory cysts seen. The standard treatment is enucleation in these cysts. Fewer reports assessed PCs application and bone grafting after cyst enucleation found to be accelerating bone healing and regeneration compared to bone graft only.[26]

CLEFT LIP AND PALATE AND ALVEOLAR CLEFT DEFECTS

Cleft lip and palate are congenital defects in maxillary and nasal processes that result in cleft lip and/or palate. Surgical closure is the treatment of choice. PRP enhances soft tissue closure of cleft palate. It also reduce the incidence of oronasal fistula. Mixing PRGF with bone grafts resulted in complete closure of 90.9% cases.[27] Alveolar clefts are congenital alveolar bone defects that affect more than three fourth of the cleft lip and palate patients. The combination of iliac graft and PRP reduce bone resorption compared to iliac graft alone in patients.

BISPHOSPHONATE RELATED OSTEONECROSIS OF JAW

Bisphosphonate Related Osteonecrosis of Jaw (BRONJ) is commonly presented with exposed necrotic bone that persists for 8 weeks or more. It is seen in patients with metastasis or osteoporosis and those who are under anti resorptive medications. PRF enhances soft tissue healing and reduce pain in surgically debrided BRONJ cases. Erbium Chromium: Yttrium Scandium Gallium Garnet laser (Er,Cr:YSGG) assessed surgery along with PRP application promote healing in these cases.[28]

OSTEORADIONECROSIS OF JAW

Osteoradionecrosis of the jaws is defined as bone necrosis caused by radiation therapy. PCs have been used in treating patient with osteoradionecrosis. The application of L-PRF combined with surgical debridement in managing cases of osteoradionecrosis, resulted in complete healing.[29]

OROANTRAL COMMUNICATION

Oroantral communication (OAC) is an abnormal communication between the oral cavity and the maxillary sinus that occur due to any pathologies or extraction of maxillary molars.[8] The treatment depends on the size of the communication and it is usually done by buccal advancement flaps. PRF clot usage enhance wound closure and reduce pain and swelling compared to buccal advancement flap. PRF membrane is used to manage OAC of size ≤5mm.

ORAL ULCERS AND POTENTIALLY MALIGNANT DISORDERS

Oral ulcers can occur in graft vs host disease (GvHD). Application of PCs gel in those patients reduces pain and accelerates healing. PRF are effective in healing post excision of oral leukoplakia, lichen planus, lichenoid reaction, pemphigus vulgaris, mucous membrane pemphigoid and other oral ulcerations which do not show dysplastic features and involving mainly epithelium (superficial lesions).

TEMPOROMANDI BULAR JOINT DISORDERS

TMDs are diseases that affect the temporomandibular joint articular surfaces, surrounding masticatory muscles. PRP injection reduces pain and improve mouth opening in these patients.[30]

CONCLUSION

The emerging science of transfusion medicine is still a growing field in which many clinical research studies are yet to be made. With the reduction in cost, the usage of PRP and PRF in dental clinic promotes safe and natural healing in surgical procedures. Its the clinicians' responsibility to gain a thorough understanding of this biotechnology and to use it correctly and wisely.

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