PRF: A Revolutionary Multipurpose Autogenic Biomaterial

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Received: June 26, 2019; Published: August 02, 2019

Abstract

Platelet play a vital role in the mechanism of wound healing. This function had prompted researchers to develop a methodology by which we could steer the healing mechanism in patients favour. The last sixty years have seen evolution of platelet concentrates to the present point where an array of techniques and instruments has been developed for this purpose. This article briefly reviews the evolution of platelet concentrates; technique, advantages, limitations and application of various types of concentrates in use currently.

Keywords: Platelets; Platelet Concentrates; Platelet Rich Fibrin; PRF Membrane; Wound Healing

Abbreviations


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History of research on blood and blood products in medical science dates back to ages. Rather, religious beliefs and phrases on blood can be found in literatures of all races and religions. Blood has been described as “Elixir of life” and the phrase does hold true in real sense. Blood and its components are pivotal from nourishing to maintenance and repair of human body.

Mechanism of wound healing and repair has been an unresolved mystery even after decades of research and many a phenomenon are still supported by single or even multiple hypothesis. In this extensive research on blood components and their individual functions and contribution to healing mechanism, a common consensus is on the lead role of platelets in this process. They are the first cells to respond
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in the process of wound healing and lay the foundation for formation of clot after injury. Additionally, the chemical mediators released by their granules help in initiation of neoangiogenesis and neocollagenogenesis.

Recognition of this role prompted researchers across the globe to develop a mechanism by virtue of which platelets could be concentrated to medically accelerate the healing process. Whitman., et al. introduced the concept of PRP almost two decades ago. This acted like a spark and ignited a research and application of platelet concentrates in healing body defects. In the beginning of 21st century, Choukroun., et al. [1] introduced a new generation of platelet concentrate termed as PRF which has gained most popularity. There are many a variants and preparation protocols, with each one having its own advantages and applications.

Types of preparations

The family of platelet concentrates can generally be divided as per following classification [2]:

1. Platelet rich plasma
   a. Pure PRP or Leukocyte poor plasma(P-PRP)
   b. Platelet and leukocyte rich plasma(L-PRP)

2. Platelet rich fibrin
   a. Pure PRF or leukocyte poor PRF(L-PRF)
   b. Platelet and leukocyte rich PRF(P-PRF)

<table>
<thead>
<tr>
<th>Year</th>
<th>Name [Reference]</th>
<th>Description</th>
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<tbody>
<tr>
<td>1986</td>
<td>Knighton [5]</td>
<td>Successfully demonstrated better wound healing and termed it as “Platelet derived wound healing factors (PTWHF)”</td>
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<td>1997</td>
<td>Whitman [6]</td>
<td>Developed and ignited interest and research in PRP</td>
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<tr>
<td>2000</td>
<td>Choukroun [1]</td>
<td>First introduced the term PRF, a completely autologous product with strong polymerisation gel. It started a new revolution in the academic and clinical research for platelet concentrates and was referred to as second generation platelet concentrate.</td>
</tr>
<tr>
<td>2006</td>
<td>Sacco [8]</td>
<td>Introduced the concept of CGF. RPM in the range of 2500-2700 was used and the fibrin clots were larger and denser.</td>
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<tr>
<td>2008</td>
<td>Everts [9]</td>
<td>Emphasised importance of leucocytes in PRF and recognised two types of concentrates; inactive concentrate as P-LRP platelet-leukocyte rich plasma and activated concentrate as PLG.</td>
</tr>
<tr>
<td>2009</td>
<td>Ehrenfest</td>
<td>Proposed first classification of platelet concentrates (discussed in detail in article)</td>
</tr>
<tr>
<td>2010</td>
<td>Sohn [10]</td>
<td>Introduced the concept of sticky bone by mixing fibrin glue with bone graft</td>
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<tr>
<td>2014</td>
<td>Choukroun [11]</td>
<td>Introduced the concept of A-PRF with more concentration of monocytes</td>
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<tr>
<td>2014</td>
<td>Tunali [12]</td>
<td>Introduced the concept of T-PRF</td>
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Table 1: Evolution of PRF.

Biochemistry of PRF

Platelets are irregularly shaped anuclear cells with the highest turnover rate amongst blood cells (half life of 7 - 10 days). Platelets are composed of an outer shell formed by phospholipid membrane which houses microtubules, an extensive canalicular system connecting the surface to the cytoplasm, mitochondria, alfa and dense granules, lysosomes and peroxisomes. Alpha granules are large macromolecules that constitute 15% of the total platelet volume. Alfa granules are believed to be the housing for chemical mediators involved in wound healing. They release growth factors like PDGF, VEGF and TGF. These growth factors are responsible for inducing cell mitosis, neo-angiogenesis and neo-collagenogenesis and promoting osteoblastic activity. The cytokines released from platelets modulate platelet activation and function and play a vital role in mechanism of inflammation. They also contribute in proliferation and differentiation of leukocytes.

A normal blood clot contains approximately 5% of platelets. This percentage multiplies by a factor of 19 in PRF which contains more than 95% platelets. The polymerisation of fibrinogen into fibrin establishes a finely knit web that holds all the healing cells and growth factors together. This fibrin meshwork also acts as a scaffold. Hence the concentrate (PRF) transplanted into the defect enriches the microenvironment with abundance of workforce deputed to the task of healing. More than 95% of the growth factors are secreted by them within 60 minutes after clotting. However, they keep synthesising and releasing growth factors for remaining life of 7 - 10 days.

PRF causes sustained release of growth factors due to its natural polymerisation structure. Release of VEGF peaks around 1 - 2 days and plays a major role in initiating neo angiogenesis. Release of PDGF peaks around 3 - 5 days and plays vital role in migration and proliferation of mesenchymal stem cells. It also has angiogenic effect on endothelial cells. TGF-beta levels peak around 5 - 7 days. It stimulates collagen type 1 formation, osteogenesis and woven bone formation.

PRF also has high concentration of entrapped leucocytes. These leucocytes release various chemokines, cytokines and opioid peptides which keeps inflammation and pain in check.

Preparation of PRF

Phlebotomy is carried out with in recommended sterile manner and blood sample is collected in glass or glass coated tube devoid of any anticoagulants. It is put in tabletop centrifuge at 3000 rpm for 10 minutes. Three layers get segregated; acellular plasma, PRF and red blood cells from top to bottom. PRF clot is withdrawn from the tube and RBC layer gently separated with scissors. Care should be taken not to over cut the clot from bottom as maximum concentration of platelets is at the bottom of PRF clot (junction of PRF and RBC layer). Clot is placed in a sterile container for around 10 minutes for the serum to leech out. This clot may now be converted into membrane by compression between two gauze packs or membrane forming sieved plates. It may also be mixed with bone graft materials if grafting is to be done.

Advantages of PRF

1. Platelet rich plasma introduced by Whitmann required addition of xenogenic thrombin. However, PRF is a much simpler procedure, requires the use of a tabletop centrifuge and is completely autogenic.
2. It causes sustained release of growth factors entrapped in the fibrin meshwork over a period of time.
3. It is believed to accelerate both soft and hard tissue regeneration and simultaneously keeping inflammatory mediators under check. It stimulates osteoblastic activity both in terms of proliferation and differentiation.
4. It has been found to possess immunological and antibacterial properties. Its use may help the patient hold post-operative infections at bay.
5. It can be used alone as a clot, or in membrane form, or in combination with bone grafts as I-PRF.
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6. PRF in membrane form has the potential to repel epithelial cells from the defect and promotes surface epithelisation making it an ideal aid for guided bone regeneration.

7. It is biodegradable and the period may range from anywhere between 7-14 days. Heat treatment may increase the longevity for up to 28 days.

8. It is an economical option in comparison to commercially available biomaterials.

Limitations

1. Limited quantity of PRF is available.
2. It requires expertise in phlebotomy to extract adequate samples
3. It may not be a good option in patients with altered coagulation profile.
4. The membrane formed gives a small coverage area.

Recent improvisations in PRF

CGF: In 2006, Sacco developed the concept of CGF. When drawn sample of blood is subjected to a specific speed in special centrifuge (Medifuge, Italy), a fibrin clot denser and richer in growth factors is obtained.

A-PRF: The role of monocytes is well known in healing of wound. Choukroun in 2014 introduced A-PRF which contains monocytes. It is functionally superior to routine PRF in terms of early promotion of soft tissue growth, faster neo-angiogenesis, and better release of growth factors and cytokines.

AFG: Extraction of AFG from blood can be achieved by subjecting the drawn sample at speed of 2400 - 2700 rpm for 2 minutes. This separates the sample into a superficial layer of AFG and deeper layer of RBC. AFG is retrieved in a syringe and is mixed with particulate graft and left alone for 5 - 10 minutes. This glue binds the graft particles together. This makes handling of the graft material much easier as well as helps in better and early osteogenesis.

I-PRF: i-PRF has been introduced recently by Mourao. It can be prepared by centrifuging at 3300 rpm for 2 minutes and the obtained reddish plasma can be injected or poured over a pre-heaped particulate graft to give it a “steak” appearance.

T-PRF: It was introduced by Tunali, et al. in 2014. It was result of a hypothesis that the silica present in centrifuge tubes used for L-PRF had the potential to be hazardous. Titanium tubes were substituted for the silica coated plastic tubes. Scanning electron and fluorescence microscopy analysis concluded that T-PRF was better organized, thicker and could cover larger area.

Applications of PRF in Oral and Maxillofacial surgery

Socket preservation

Various studies have shown the positive impact of PRF in accelerating and preserving the ridge after extraction. Higher bone density was achieved in sockets packed with PRF [14,15].

Third molar surgery: prevention and treatment of dry socket

A meta analysis [16] concluded that local application of PRF after third molar surgery relieves pain and 3 day post operative swelling reducing the incidence of dry socket. The introduction of PRF plug in the existing dry socket case is proven to cause significant fall in pain score. However, another meta analysis study could not establish any advantage of using PRF [17].

**Case 1: Extraction of third molar.**

*Figure 1.1:* Preoperative picture.

*Figure 1.2:* PRF plug insertion after surgical removal.

**Citation:** Ujjwal Gulati, *et al.* "PRF: A Revolutionary Multipurpose Autogenic Biomaterial". EC Dental Science 18.9 (2019): 1977-1999.
Packing bone defects after cyst enucleation or apicoectomies

PRF plug helps in obliterating the dead space. It also accelerates osteogenesis with higher bone density [18].

**Case 2: Cyst enucleation**
Figure 2.2: Coronal section showing extent of the cyst.

Figure 2.3: Sagittal section showing extent of the cyst.
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Figure 2.4: After enucleation of the cyst.

Figure 2.5: PRF clots packed in the cavity.

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**Case 3:** Enucleation of cyst and extraction of teeth.

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Figure 3.2: Sagittal section showing cyst involving mandibular second and third molars.

Figure 3.3: Post-extraction and cyst enucleation.

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Figure 3.4: A-PRF prepared.

Figure 3.5: PRF plug insertion.

Along with bone graft

There are multiple advantages as well as techniques of using PRF or its variants with bone grafts. Minced PRF with graft particles act as a biological connector between the graft particles. The exudate expressed out of PRF and after mincing is better than using saline for “wetting” of graft. It causes sustained release of growth factors which creates a favourable environment for grafted wound healing. The AFG has been used to enhance the handling characteristics of graft material. It helps in formation of “sticky bone” which can be easily carried to the site and has lesser chances of displacement while membrane stabilisation or suturing [19].

Case 4: Immediate implants and GBR.

Figure 3.6: Closure.

Figure 4.1: Extraction and implant insertion.
**Figure 4.2**: PRF plugs and Xenograft mixed with minced PRF membrane and wetted in PRF Exudate.

**Figure 4.3**: Graft and Membrane in place.

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Figure 4.4: Membrane stabilized with sutures and layered with PRF membranes.

Figure 4.5: Final closure.

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Case 5: Implant, sinus lift and foreign body removal.

Figure 5.1: Pre-operative IOPA.

Figure 5.2: Implant osteotomy with sinus lift and foreign body removal.

Figure 5.3: Foreign body.

Figure 5.4: Xenograft mixed with minced PRF and PRF clots.

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Figure 5.5: Sinus grafted.

Figure 5.6: Sinus window closed with PRF membrane.

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**Figure 5.7:** Post-operative IOPA.

**Case 6:** Immediate extraction and implant.

**Figure 6.1:** Pre-operative clinical view.

Figure 6.2: Extracted root stump.

Figure 6.3: CBCT coronal section.
Figure 6.4: Extraction and placement of implant without raising flap.

Figure 6.5: Space between socket walls and implant grafted.
Figure 6.6: PRF membrane.

Figure 6.7: PRF membrane sutured over the Graft.

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Sinus membrane repair

PRF membrane and A-PRF can be used to repair small perforations in sinus membrane [20].

Augmentation of sinus floor

PRF is a good option and acts as an alternate to bone grafts in case of crestal sinus lift. It has dual advantage; it guards against the impact of osteotomes and if any perforation occurs it may help in sealing the defect. A systematic review concluded that PRF could be used as sole grafting material with simultaneous implant placement. PRF could accelerate maturation of demineralised freeze dried bone allograft but had no effect on deproteinized xenograft maturation. PRF membrane could be used to cover sinus membrane and osteotomy window [21].

Periodontal bone defects

A systematic review on effect of PRF in curing intra bony defects concluded that use of PRF resulted in better outcome than open flap debridement alone. Also, PRF could augment the efficacy of bone graft used for intrabony defects [22].

As membrane for coverage of raw areas on both keratinised and non-keratinized tissue

The raw defects after surgical excision of oral lesions and fibrotomy in OSMF can be covered with PRF membranes. This is proven to offer better healing with lesser postoperative pain [23].

Conclusion

PRF has proven to be a break point in search for a user friendly autogenic biomaterial. It involves minimal operating cost after a onetime expense on the respective tabletop centrifuge. The quest has not ended and last decade has seen many a variations being introduced and successfully incorporated into practice. There can be differences of opinion on the magnitude of advantages this biomaterial offers and limitations it has, nonetheless it is the only biomaterial where we are not talking about negative outcomes like rejection and infection.

Bibliography


Volume 18 Issue 9 September 2019
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