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FIBRIN GLUE in SURGERY: A CASE SERIES and CRITICAL REVIEW

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Running title: Platelet Rich Fibrin- Role and its Applications

Clinical Significance: There are a large number of clinical indications of PRF in oral and maxillofacial surgeries, plastic surgeries, small otology surgeries for the improvement of soft tissue healing, bone graft protection, and remodeling.

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ABSTRACT

'Fibrin Glue', or the Platelet-rich fibrin (PRF), is a second-generation platelet-concentrate that has shown to promote soft tissue healing, as it contains within its tetramoloecular structure; autologous growth factors, circulating stem cells, platelets, leucocytes and cytokines, which help in bone regeneration and in the maturation of soft tissues. It is prepared from the patient's blood. The cost of the regeneration therapy is drastically reduced and the time spent in the procedure is less, and therefore beneficial for both the surgeon and the patient.

Key words: Reconstructive Surgery; Platelet Rich Fibrin; Grafting Materials; Bone replacement

INTRODUCTION

Platelet concentrates are innovative tools of regenerative medicine that have been used in a large number of surgical, regenerative, periodontal and plastic surgery cases, and its performance is still under scrutiny. [1]

Tentative usage of PRF:

- in extraction socket preservation,
- sinus augmentation,
- sinus lift procedures for implant placement,
- intrabony defects and bone augmentation,
- root coverage procedures,
- reduction in swelling and edema after 3rd molar surgery
- healing in donor site with successful results.[2]
- prevention and treatment of bleeding in severe thrombocytopenia cases,
- severe oral hemorrhage associated with medullary aplasia, acute leukemia, etc. [3] used as a bioactive surgical additive.[4]
- sealing of wound borders and the
- facilitation of cutaneous reapplication in general and plastic surgery.[5]These adhesives are also used in oral and maxillofacial surgery.[6-8]

Contents of PRF

PRF is a fibrin- rich gel, produced from the extracted venous blood of the patient that has undergone a single centrifugation. This centrifugation causes the cells to settle down in different layers; and it is the middle of the lowest layer of the red blood cells, that is picked up. As per the experiments conducted by various authors, it was observed that the platelets and the leucocytes were collected in the fibrin meshwork of the PRF. The plasma layer was found above this. The plasma rich fibrin (PRF) was also

found to trap both clotting factors and cytokines within its fibrin network. Neither anticoagulants nor natural blood clotting process was used for the PRF formation as the whole process is done at the normally required pace, controlled by centrifugation. PRF layer also contains platelets and plasma.[9]

Observation by using the photonic microscopy revealed that the platelets and leukocytes, distributed within the clot, was not uniform. They were located in the intermediate layer, between the RBCs and fibrin clot, and were represented by a macroscopic buffy coat on the PRF-clot surface. Hence, it is the whitish layer that has to be used by practitioners, for their surgeries, when harvesting clots for surgical use. It is mandatory to preserve a small RBC layer at the clotting end of the PRF to collect as many leucocytes and platelets as possible. An accurate knowledge of the clot structure, for which scissors are used, would be helpful in proper PRF preparation. This insight is deemed useful, as the two ends of the PRF have different properties and benefits.

The SEM studies observed that the RBCs were principally located in the red part of the PRF clot, and the leukocytes, in between the junction of the red and yellow parts of the clot. The rest of the clot contained only a few RBCs and even they were probably artefacts that occurred during clot handling. The altered morphology of the platelets was said to occur during the aggregation and clotting process. Kawasaki et al. observed similar findings with thrombin-activated PRP and observed that the platelets made the fibrin meshwork rigid.

Due to the condensation of the fibrin meshwork, the PRF-membrane had fibrin strands that were condensed and stuck to each other. They were denser than a blood clot or even a common PRP (platelet rich plasma). During wound closures, the clots resorbed extremely slowly, owing to the slow remodeling process of the fibrin meshwork into a healed mass.[10]

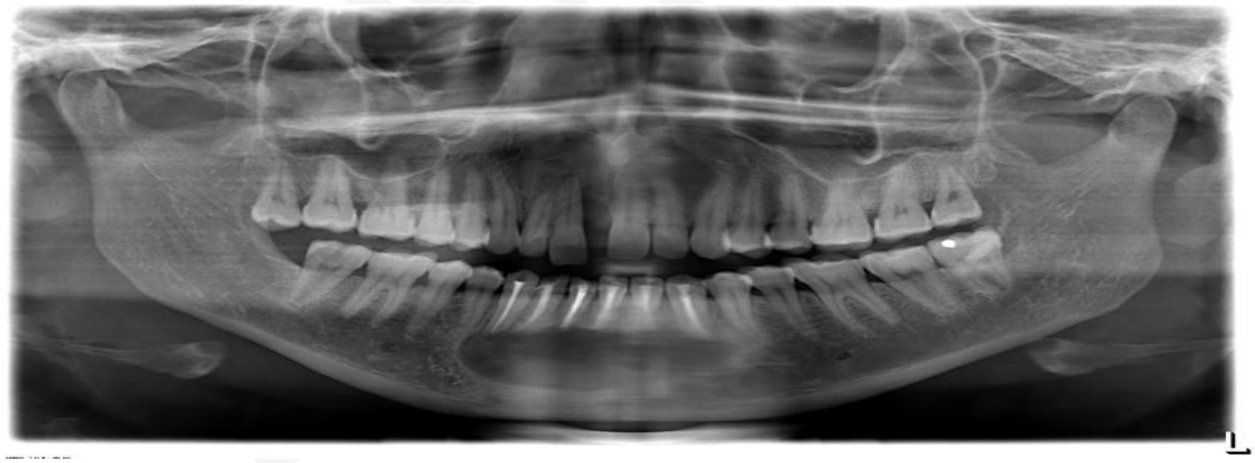
Autologous bone regeneration is produced by various methods. Concentrated platelets are one of them. The concentrated platelets are predominantly made up of growth factors such as platelet-derived growth factor (PDGF); transforming growth factor β
(TGF- β); [11] and vascular endothelial growth factor (VEGF), and an important coagulation glycoprotein (thrombospondin-1, TSP-1); within 7 days.[2] It also contains IL-1b, IL-6, and TNF-α, which stimulates many biological functions such as angiogenesis, chemotaxis, differentiation, proliferation, modulation, and is, therefore, a possible therapeutic device for a more speedy and successful regeneration of hard and soft tissues. [12]

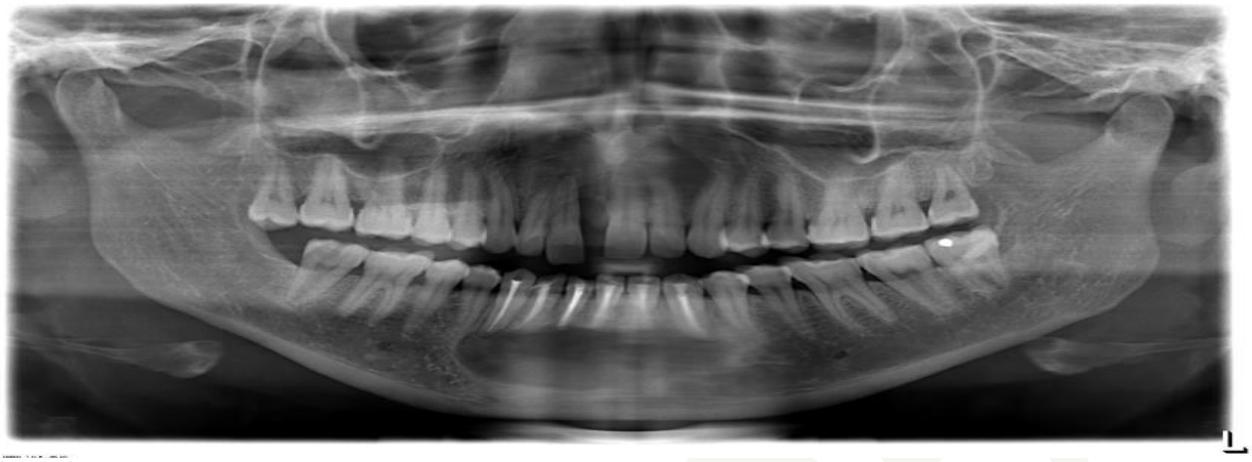
CASE REPORT

Case 1 –

A female patient, aged about 40 years; had a clinically, radiologically and histologically confirmed radicular cyst, in relation to her lower right lateral incisors. Enucleation followed by apicectomy was done. This was followed by the PRF placement at the surgical site

Preoperative and Postoperative OPG (Orthopantomogram)

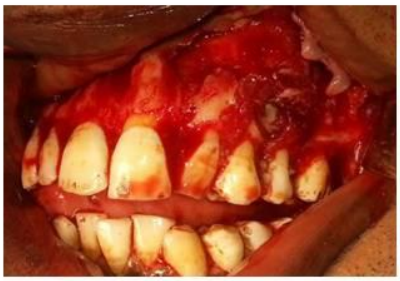
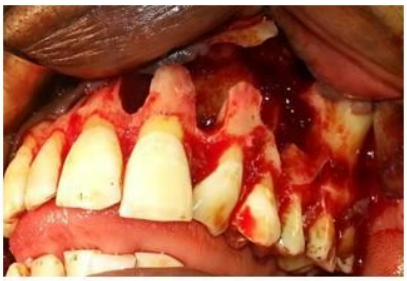
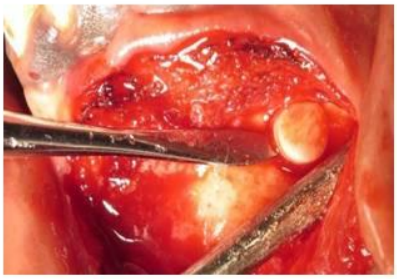
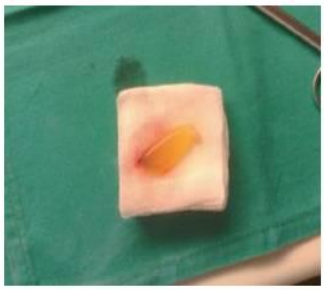


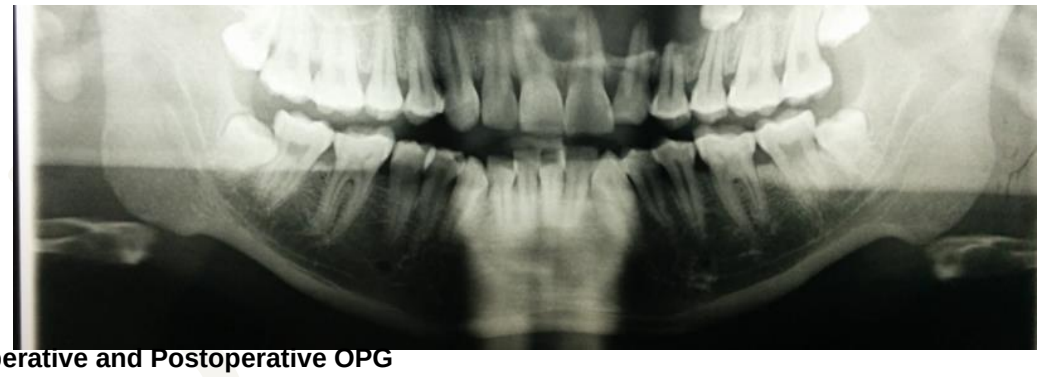


Platelet rich Fibrin

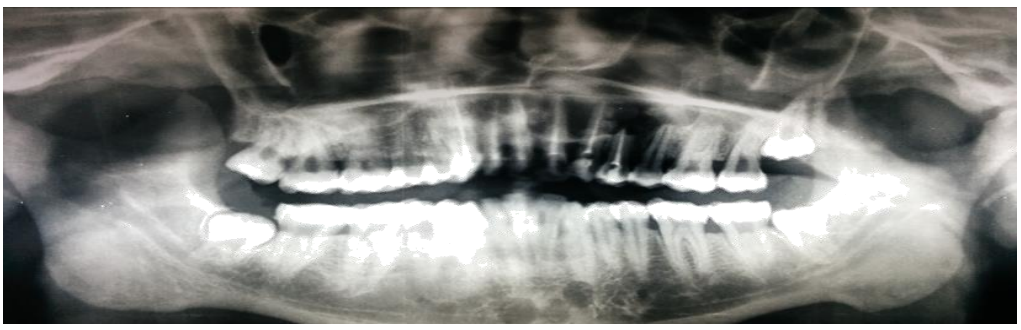
Case 2

A male patient, aged about 26 years, had an impacted upper left canine. Surgical extraction was done under local anesthesia and PRF membrane was used in the socket, post extraction.



Preoperative and Postoperative OPG



DISCUSSION

History:

Choukroun, et al., in France, first developed PRF, for use in oral and maxillofacial surgical cases.[10]This technique required neither an anticoagulant nor bovine thrombin (nor any other gelling agent). It was a centrifuged blood without any additives. [13]

In 1974, the regenerative potentiality of platelets was understood, and Ross et al.[14] were first to describe the generation of a growth factor from platelets. Evolution of the bone regenerative stem cell materials first started with the advent of PRP from the late 1990s in the last century, which was followed by the release of the second generation of platelet aggregates; platelet-rich fibrin (PRF), and recently by the advanced platelet rich fibrin clot (a-PRF).[2]

Method of preparation

The concentrated platelets in PRP are created by centrifugation of approximately 1 million platelets per 1 mm^3.

PRF in addition to the concentrated platelets also contains an autologous fibrin meshwork that inhibits the growth factors from undergoing proteolysis, as stated by Lundquist. The placement of dental implant is normally done after 12-weeks of bone grafting, and if the healing of the bone graft was accelerated, it shortened the time for dental implant placement; therefore shortening the time in which the patient would remain edentulous.[9]

Platelet-rich Fibrin is a natural fibrin based biomaterial without any artificial biochemical modifications[13]. It eliminates the risk of disease transmission; and besides, its jelly-like consistency favors stability of the clot and the grafting material. This natural material accelerates the physiological wound healing and together with bone grafts, it seems to accelerate the new bone formation[11, 15, 16, and 17].

Preparation of the fibrin mesh:

The protocol for PRF preparation is very simple and simulates that of PRP.

- It includes collection of venous whole blood (around 5 ml) in each of the two sterile vacutainer tubes (6 milliliter) without anticoagulant and
- the vacutainer tubes are then placed in a centrifugal machine at 3,000 revolutions per minute (rpm) for 10 min,

after which it settles into the following three layers:

  - Upper straw-colored acellular plasma,
  - the red-colored lower fraction containing red blood cells (RBCs), and
  - the middle fraction containing the fibrin clot.

- The upper straw-colored layer is then removed, and middle fraction is collected, 2 mm below to the lower dividing line, which is the PRF.
- The mechanism involved in this is; the fibrinogen concentrated in the upper part of the tube,

combines with circulating thrombin formed due to centrifugation, to form fibrin.

- A fibrin clot is then formed in the middle, between the red corpuscles at the bottom and acellular plasma at the top. The middle part are platelets, trapped for the most part, in fibrin meshes.[16]
- Platelet concentration seen in PRP is not seen in the PRF. There is a closer resemblance to a wound response in PRF. There is a formation of a 3-dimensional cross-linked fibrin matrix, which serves as a binding site for both platelets and GFs.[16]
- The success of this technique entirely depends on time gap between the blood collection and its transfer to the centrifuge and therefore it should be done in less time possible.
- The blood sample without anticoagulant starts to coagulate almost immediately, upon contact with the glass, and it decreases the time of centrifugation to concentrate fibrinogen.
- Resistant autologous fibrin membrane is then available, by driving out the fluids trapped in fibrin matrix.[4]
- Following the proper protocol and quick handling, a clinically usable PRF clot charged with serum and platelets is obtained. Simplified processing technique without any complex handling makes it superior to PRP.

NOTE:

- Additives like thrombin are not essential in PRF as it has its own fibrin meshwork.[9]
- The release of growth factors are time bound and released slowly, taking approximately 5-7 days as suggested by Marx.[4]
- Ling has suggested a longer role for the PRF in osteoblast stimulation as compared to the other bone regenerators.[9]
- The production method of PRF was first introduced by Choukroun.

Advantages of PRF over PRP:

PRF can be used to promote wound healing, bone regeneration, graft stabilization, wound sealing, and hemostasis. Because the fibrin matrix is better organized, it can efficiently direct stem cell migration and healing.

The release of growth factors from PRF, in-vitro and in-vivo, led to studies that optimized the clinical application of PRF.

Better results were seen in the case of PRF as compared to the PRP.

- Dohan et al.[13] exhibited that a slower release of growth factors from PRF than PRP, and observed better healing properties with PRF. It was observed and shown that the cells were able to migrate from fibrin scaffold; some authors established the PRF, as a supportive matrix for bone morphogenetic protein as well.

- PRP systems require a large volume of blood, yet produce only a small volume of PRP.
- More importantly, most PRP systems rely on animal-derived thrombin to initiate platelet degranulation, and no system has shown a sustained growth factor release.[16]

CONCLUSION

The clinical experience confirms that PRF can be considered as a healing biomaterial. It contains all the necessary parameters that assist in optimal healing. However, the numerous perspectives of PRF have still to be clinically tested, and more studies are needed to correlate clinical outcome with the biologic mechanisms.

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Ethical consent: The authors have obtained the permission from the ethical committee of the institution to conduct the studies

Patient consent: The consent of the patients has been obtained prior to the procedure for conduct and publication of the study.

ABBREVIATIONS

PRP----------Platelet rich plasma

PRF----------Platelet rich fibrin

SEM----------Scanning electron microscope

TGF-β----------Transforming growth factor-β

PGDF----------Plasma derived growth factor

VEGF----------Vascular endothelial growth factor

TSP-1 ----------Thrombospondin-1

IL-1b----------Interleukin-1b

IL-6----------Interleukin-6

TNF-α----------Tumor necrosis factor α

a-PRF----------Advanced platelet rich fibrin clot

mm^3----------Cubic millimeter

rpm----------Revolutions per minute

GF----------Growth factor

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