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Review Article

Platelet Rich Fibrin – Evolution and Application in Oral and Maxillofacial Surgery

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Abstract: Platelet-rich fibrin (PRF) was first described by Choukroun *et al.* in France. It has been referred to as a second-generation platelet concentrate, which has been shown to have several advantages over traditionally prepared PRP. It's a new generation of platelet concentrates geared to simplified preparation without biochemical blood handling. This article describes the evolution of this novel platelet concentrate and its applications in the field of Oral and Maxillofacial Surgery.

Keywords: Fibrin, Growth factors, Platelet-rich fibrin (PRF), Natural Tissue Regeneration(NTR)

INTRODUCTION

The use of platelet concentrates in tissue regeneration is a developing area for clinicians and researchers and has been employed in various fields of surgery.

Platelet-rich fibrin (PRF) is an immune and platelet concentrate collecting on a single fibrin membrane,with all the constituents of a blood sample, favourable to healing and immunity [1-3].

Platelet rich fibrin (PRF) is a fibrin matrix in which platelet cytokines, growth factors, and cells are trapped and may be released after a certain time and that can serve as a resorbable membrane. Choukroun and his associates were amongst the pioneers for using PRF protocol in oral and maxillofacial surgery to improve bone healing in implant dentistry. Autologous PRF is considered to be a healing biomaterial, and presently, studies have shown its application in various disciplines of dentistry.

This article will focus on the basic science, evolution and clinical application of Platelet rich fibrin in Oral and Maxillofacial Surgery.

Platelet rich fibrin - Evolution

In transfusion medicine, platelet concentrates were originally used for the treatment and prevention of haemorrhage due to severe thrombopenia, which is often caused by medullar aplasia, acute leukaemia or to counter significant blood loss occurring during surgery. The standard platelet concentrate for transfusion has been named platelet-rich plasma (PRP).

The use of blood-derived products to seal wounds and stimulate healing started with the use of fibrin glues, which were first described 40 years ago and are constituted of concentrated fibrinogen (polymerization induced by thrombin and calcium). Autologous fibrin glues are considered the best choice to avoid contamination risk, but their use remains very limited owing to the complexity and the cost of their production protocols [4-5].

The development of platelet concentrate technologies offers simplified and optimized production protocols for a new kind of fibrin adhesive, concentrated platelet-rich plasma. Whitman *et al* [6] have described platelet-rich plasma as an "autologous alternative to fibrin glue". Platelets contain high quantities of key growth factors, such as PDGF (platelet- derived growth factor), TGFb-1 (transforming growth factor b-1) and VEGF (vascular endothelial growth factor), which are able to stimulate cell

proliferation, matrix remodelling and angiogenesis, The use of these growth factors to enhance healing is an interesting option. Indeed, these concepts have spurred their commercial exploitation with the development of a wide range of preparation protocols, kits and centrifuges.

In recent times, a variety of platelet concentrates has been developed and has shown promising results. Platelet concentrates have been developed with an idea to combine the fibrin sealant properties with the growth factors in platelets thereby providing an ideal base for wound healing and regeneration of tissues [7] Platelet rich plasma (PRP), the first generation platelet concentrates showed positive results, however, the complexity of PRP preparation protocol and the risk of cross-infection due to the use of bovine thrombin led to development a newer generation of completely autologous platelet concentrates, platelet rich fibrin also called as Choukroun's platelet rich fibrin named after its inventor.

Platelet rich fibrin, the second generation platelet concentrate was developed in France by Joseph Choukroun et al. in 2001. They used PRF to improve bone healing in cases of implants. It is a fibrin matrix in which platelet cytokines, growth factors and cells are trapped and may be released after a certain time and that can serve as a resorbable membrane. Growth factors are released after activation from the platelets trapped within fibrin matrix, and have been shown to stimulate the mitogenic response in the periosteum for bone repair during normal wound healing [8].

Preparation of PRF

Choukroun's PRF (platelet-rich fibrin) is the second generation platelet concentrate. Here, blood is collected without any anticoagulant and immediately centrifuged. A natural coagulation process then occurs and allows for the easy collection of a leucocyte- and platelet-rich fibrin (L-PRF) clot, without the need for any biochemical modification of the blood, that is, no anticoagulants, thrombin or calcium chloride are required. This open-access technique is the most simple and also the least expensive protocol developed so far [9].

Technique

The PRF protocol is very simple: A blood sample is taken without anticoagulant in 10-mL tubes which are immediately centrifuged at 3000 rpm for 10 minutes.

The absence of anticoagulant implies the activation in a few minutes of most platelets of the blood sample in contact with the tube walls and the release of the coagulation cascades. Fibrinogen is initially concentrated in the high part of the tube, before the circulating thrombin transforms it into fibrin. A fibrin clot is then obtained in the middle of the tube (Fig 1 and 2), just between the red corpuscles at the bottom and acellular plasma at the top. Platelets are theoretically trapped massively in the fibrin meshes [10].

Fig. 1

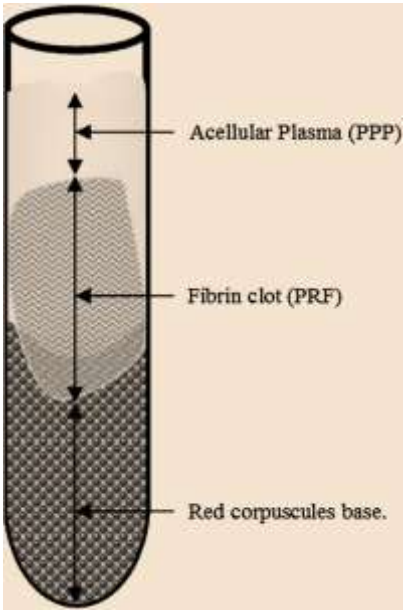

Fig. 2

Layers of PRF

PRF results from a natural and progressive polymerization which occurs during centrifugation [11]. The success of this technique entirely depends on the speed of blood collection and transfer to the centrifuge. Indeed, without anticoagulant, the blood samples start to coagulate almost immediately upon contact with the tube glass, and it takes a minimum of a few minutes of centrifugation to concentrate fibrinogen in the middle and upper part of the tube. Quick handling is the only way to obtain a clinically usable PRF clot.

If the duration required to collect blood and launch centrifugation is overly long, failure will occur: The fibrin will polymerize in a diffuse way in the tube and only a small blood clot without consistency will be obtained [8].

PRF membrane can also be obtained by driving out the fluids trapped in the fibrin clot. Fluid removal from the PRF fraction can be done through mechanical pressure between gauze layers resulting in a fairly solid, gel-like material that can be used in various clinical applications as a filling material or as a suturing membrane [12].

Why PRF over PRP?

1. Low cost and the great ease of the procedure.
2. It allows the production of many concentrates quickly and by natural means, that is, without the use of chemicals or unnatural conditions.
3. Unlike the PRPs, Choukroun's PRF does not dissolve quickly after application; instead the strong fibrin matrix is slowly remodelled in a similar way to a natural blood clot. Platelets and leucocytes are collected with high efficiency in this method and leucocytes are preserved throughout. However, platelets are activated during the process, which leads to a substantial embedding of platelet and leucocyte growth factors into the fibrin matrix [13, 14].
4. Fine and flexible 3-D structure of PRF more favourable to cytokine enmeshment and cellular migration.3-D network-connected tri-molecular or equilateral junctions in PRF allows the establishment of a fine and flexible fibrin network able to support cytokines enmeshment and cellular migration, while 3-D organization of PRP consists of a fibrin network condensed tetra molecular or bilateral junctions constituted with strong thrombin concentrations which allows the thickening of fibrin polymers leading to a rigid network, not very favourable to cytokine enmeshment and cellular migration [7].
5. PRF helps in haemostasis [15].

PRF in Oral and Maxillofacial Surgery

When considering the functions of PRF related to tissue regeneration, we can anticipate its role to be throughout all areas that require healing and regeneration. Especially when the generation of new blood vessels, the proliferation and differentiation of fibroblasts and osteoblasts, and the anti-inflammatory functions are considered, PRF can be used in socket preservation, bone regeneration with/without implant, sinus lift (lateral, crestal approach), dressing agent and gingival surgery.

PRF in alveolar sockets and cyst cavities

Tooth extraction or avulsion is logically the most important and common surgical situation encountered in oral and maxillofacial surgery, and as old as human kind itself. This surgical procedure is more or less complex, but the outcomes are globally good. The use of a surgical adjuvant may seem unnecessary, but there are 3 configurations where a healing booster may be highly interesting.

1. Post surgical follow up following complex extractions or third molar surgery, being very often associated with pain and swelling [16].
2. The second situation is when implant restoration is considered after avulsion [16].
3. The third situation is the avulsion in patients with general or local pathologies that interfere with bleeding or healing. Particularly true in patients on anticoagulants/bisphosphonates [16].

The systematic use of a platelet concentrate in order to avoid painful events, promote bone regeneration and improve gingival healing may become a relevant principle in oral surgery.

The plugs and membrane can be used to fill avulsion sockets, even when associated with severe cystic destructions after cyst exegesis [17, 18], and allow a quick bone and gingival regeneration required for implant placement. It can also be mixed with a bone substitute and used as a protective cover over the grafted area, this is particularly important when gingival wound closure is impossible or difficult with the sutures. The function of the PRF membranes is then to stimulate gingival healing, but also to protect the bone graft from the oral environment and to maintain it within the avulsion socket, like a biological barrier, it is then not necessary to use more complex protocols for the protection of the filled socket (such as Guided Bone Regeneration (GBR) membranes and complex incisions, flaps and sutures) presenting high risks of negative outcomes. Finally, the L-PRF technique is open-access and thus can be widely developed in private practice without commercial considerations.

Whatever the technique, platelet concentrates may be considered as an efficient option for the preservation of alveolar ridges, and the systematic filling of the avulsion sockets with a PRP gel or a PRF may become a standard procedure for a high-quality oral surgery in many situations. However, even for the user-friendly and inexpensive L-PRF technique, the choice of using systematically L-PRF in all avulsions remains highly dependent on the way of working and the philosophy of the surgeon.

PRF and Tissue regeneration

L-PRF is an autologous strong fibrin membrane, loaded with autologous cells (leukocytes,

circulating stem cells) and enriched with growth factors and matrix proteins that are released during at least 7 days [19]. Such a membrane holds intrinsically all the solutions to the problems encountered with classical Guided Tissue Regeneration(GTR) techniques.

L-PRF membranes have strictly no contraindications, they can be used in all kinds of patients, they always promote soft tissue healing and they can stimulate the healing of a damaged flap and reduce the risks of flap necrosis after a surgery. It is a common point with all fibrin-based products, particularly the fibrin glues used for the stimulation of angiogenesis and to reduce the risk of flap necrosis in many general surgery applications [20].

The concept of NTR(Natural Tissue Regeneration) is to promote the regeneration of the various periodontal tissues required for a normal tooth function (bone, periodontal ligament, gingival attachment) with L-PRF membranes as filling material and protection membrane, most times in association with a bone biomaterial.

The difference between GTR and NTR is not only the replacement of the various heterologous membranes used in GTR by a new kind of natural autologous membrane; it is also a true evolution of the concept behind. Indeed, L-PRF membranes are optimized blood clot, and therefore their interactions with the tissues do not follow strictly the core principles of GTR, GTR membranes had to stabilize the blood clot and to create a cell-proof barrier against soft tissue invagination, a NBR membrane is the blood clot itself (therefore rich in cells) and is only a bioactive competitive barrier.

While other membranes are considered as foreign bodies by the host tissues and interfere with the natural tissue healing process, an L-PRF membrane is as natural as the host tissue, it is a blood clot prepared in an optimized form and that can be easily handled by a surgeon [16].

Sinus Lift

The number of publications pertaining to use of PRF in sinus-lift is quite limited, but the published data are homogeneous. Choukroun *et al.*[21], in their study on maxillary sinus lift involving PRF and a lateral approach, used freeze-dried bone allograft (FDBA) and PRF. PRF was added to FDBA particles (test group), and FDBA without PRF was used (control group). They reported that the addition of L-PRF to a freeze-dried bone allograft (FDBA) allowed obtaining after 4 months the same histological bone healing and remodelling as that of FDBA alone after 8 months.

The same technique of FDBA/LPRF combination were used in a series of 20 patients with bilateral sinus-lifts before implantation, and the implant survival rate was 100% after 5 years in these complex cases of global maxillary rehabilitation [22,23].

Finally, the use of L-PRF as sole filling material in the sub sinus cavity with simultaneous implant placement promoted the large bone regeneration around the implants, as it was proven with histologic and radiologic analyses [24-26].

Dressing agent

By taking advantage of the anti-inflammatory effects of cytokines, PRF can be used to aid the healing of the socket or for the treatment of inflammation around implants [23]. In patients on anticoagulant drugs, PRF can be used to be filled in the socket after a dental extraction without discontinuing the drugs. Such patients can anticipate haemostatic effects, reduced pain after extraction and prevention of dry socket.[27] Also, due to the enhancement of quality and thickness of the periosteal and gingiva, in addition to the bone regeneration ability, PRF is useful in regenerating periodontal tissue around implants [23, 28].

Gingival Surgery and PRF Membranes

Contrarily to the various PRP gels used as surgical adjuvant, PRF membranes present a strong fibrin matrix and are thus easily handled like a soft tissue graft during a periodontal surgery. The L-PRF membrane can be tailored and sutured, and this specific form opens a wide range of possibilities, particularly in gingival surgery where very thin grafts, flaps or membranes are commonly handled: tissue manipulation is the key concept in gingival surgery, and a L-PRF membrane is a solid tissue with a matrix and cells, and thus perfectly fits to this purpose [29].

CONCLUSION

The literature on platelet concentrates for topical use in oral and maxillofacial surgery is nowadays prolific and particularly developed in periodontology and implant dentistry, large fields of research remaining still unexplored in the maxillofacial area. In the near future, simple, efficient and inexpensive techniques like the L-PRF will logically remain the major protocols used in oral and maxillofacial surgery.

Finally, it is also important to understand that whatever the product, these preparations rich in growth factors are not magical, and their successful use is completely dependent on the skills of the surgeons and their abilities to understand, prepare, use and combine correctly the technologies.

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