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Implications of Platelet-Rich Fibrin in Oral and Maxillofacial Surgery: A Review

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ABSTRACT

Platelet-rich fibrin (PRF) is a second-generation platelet concentrate that is superior to PRP due to its mechanical and non-biochemical preparation and ability to slow down proteolysis and the rapid degradation of growth factors. The original preparation was used to produce various PRF variants; including sticky bone, advanced PRF (A-PRF), and injectable PRF (I-PRF). PRF is formed by fractioning autologous blood into elements that enhance wound healing and elements that do not, which are suspended in a fibrin matrix for preservation and slow release during healing. PRF is a flexible fibrin clot that can be tailored to a variety of tissue defect forms and can be prepared without anticoagulation. It can be molded into pellets, divided into smaller pieces, mixed with bone grafts, or flattened and utilized as a membrane. PRF is an osteoconductive scaffold that can be used to reconstruct cystic lesions and promote bone reformation. In addition, PRF can enhance wound healing and improve ridge preservation by introducing growth factors, angiogenic cytokines, and positive inflammatory cytokines. PRF in secondary alveolar cleft bone grafting (SABG) was found to improve gingival zenith when combined with iliac crest bone grafts. Studies have shown that I-PRF and A-PRF with iliac bone grafts in SABG reduce postoperative bone resorption, provide higher bone density, and provide functional and aesthetic support.

Keywords: *Platelet-rich fibrin ; Platelet concentrates ; Oral surgery ; Oral and maxillofacial surgery*

Platelet-rich fibrin (PRF) was firstly introduced by Choukroun et al (Choukroun, Diss, 2006) in 2006. PRF was deemed as the second generation platelet concentrate. (Choukroun, Diss, 2006, (Dohan, Choukroun, 2006) It has been demonstrated to be superior to the first generation platelet-rich plasma (PRP). (Dohan, Choukroun, 2006) The absence of biochemical handling of the blood and simplified preparation of PRF were major differences when compared to PRP. (Sunitha Raja and Munirathnam Naidu, 2008) Additionally, it was shown that the addition of bovine thrombin to PRP preparation could have harmful effects on body cells. (Saruhan and Ertas, 2018) The preparation of PRF, on the other hand, was thought to be a mechanical and non-biochemical process that did not include thrombin addition. (Saruhan and Ertas, 2018) Moreover, the fibrin meshwork created within PRF was claimed to slow down proteolysis and the rapid degradation of growth factors, in contrast to PRP which was demonstrated to rapidly release growth factors just before cell outgrowth from the surrounding tissue. (He, Lin, 2009) Therefore, the activity of the growth factors could be retained for a longer time due to controllable, long-term growth factors release. (He, Lin, 2009)

Prepared PRF is formed in a gel-like form that could be utilized in association with bone substitutes. (Choukroun, Diss, 2006) The combination showed a number of benefits including better bone maturation and

growth, stable grafting, suitable wound closure and hemostasis, and better handling of the graft materials. (Choukroun, Diss, 2006, (Saruhan and Ertas, 2018) In addition, PRF could be pressed into a membrane that could be used for guided bone regeneration (GBR). (Movahedian Attar, Naghdi, 2017) Clinical investigations have also highlighted the potential to improve bone quality and quantity by mixing PRF with bone grafts. (Movahedian Attar, Naghdi, 2017, (Sunitha Raja and Munirathnam Naidu, 2008)

1. History and evolution of PRF

In the 1970s, Matras (Matras, 1970) investigated skin healing in rats. He suggested using what he called "fibrin glue" in a variety of preparations to promote healing. The sticky fibrin glue had minimal anticoagulant effects, and was unable to yield reliable results. (Matras, 1970) Thereafter, a multitude of studies involving platelet concentrates in glue or gelatin forms in general surgery, neurosurgery, and ophthalmology had grown. (Agrawal, 2017, (Fan, Perez, 2020) Considering platelet concentrates in oral and maxillofacial surgery, it had been aroused in 1998 when Marx et al (Marx, Carlson, 1998) demonstrated that bone growth increased when bone grafts were infused with highly-concentrated platelet solution.

In 2000, Choukroun et al (Choukroun, Adda, 2000) used a platelet-rich concentrate form that was stiffer in consistency to finally coin the term PRF. In the 2 decades that came after, the original preparation was built upon to produce the PRF variants currently accessible, including sticky bone (autologous PRF mixed with bone graft) by Sohn et al (Sohn, Huang, 2015), advanced PRF (A-PRF) by Choukroun and Ghanaati (Choukroun and Ghanaati, 2018), and injectable PRF (I-PRF) by Mourão et al. (Mourão, Valiense, 2015)

2. Mechanism of action of PRF

The body goes through three stages when attempting to heal itself: the inflammatory phase, the proliferative phase, and the remodeling phase. (Fan, Perez, 2020) The inflammatory phase is an acute inflammation response to injury. (Fan, Perez, 2020) Blood is the vector that carries these inflammatory cells to injury site. (Karimi and Rockwell, 2019) White blood cells and platelets release crucial cellular mediators that start the healing process in addition to phagocytes that clean the wound. (Fan, Perez, 2020) These growth factors that are released include transforming growth factor beta (TGF-β), platelet-derived growth factor (PDGF), and vascular endothelial growth factor (VEGF), which regulate cell migration, proliferation, and differentiation. (Fan, Perez, 2020, (Karimi and Rockwell, 2019)

Additionally, platelets release coagulation factors that guarantee initial hemostasis. (Sunitha Raja and Munirathnam Naidu, 2008) After 24 to 48 hours, due to the existence of the inflammatory cocktail of cellular signals produced during the inflammatory phase, the proliferative phase takes control. (Sunitha Raja and Munirathnam Naidu, 2008) Fibroblasts, leukocytes, macrophages, and mesenchymal stem cells can now proliferate in order to lay the first tissue-building bricks. (Fan, Perez, 2020) Depending on the severity of the defect and the body's immune system, transition to the healing remodeling phase will take place once the first laid down tissues have been stabilized. (Karimi and Rockwell, 2019)

PRF is formed by fractioning autologous blood into elements that enhance wound healing and elements that do not. (Choukroun, Diss, 2006) By centrifuging, elements that promote wound healing are suspended in a fibrin matrix for preservation and slow release during healing. (Choukroun, Diss, 2006) The red blood cells (RBCs) are typically spun out during the centrifuging, while the white blood cells (WBCs), platelets, and fibrin are preserved. (Karimi and Rockwell, 2019) Per volume, these wound healing-enhancing components were found at much higher levels than physiologic levels. (Karimi and Rockwell, 2019) Aiming to maintain as many white blood cells and platelets while excluding as few red blood cells as feasible, PRF preparation processes were refined. (Choukroun and Ghanaati, 2018)

The fibrin matrix was proposed to be the main benefit of PRF versus PRP. (He, Lin, 2009) It was shown to act as a 3D scaffold for the leukocytes, platelets, and their release products. (He, Lin, 2009) The matrix was stated to allow for gradual release of its contents so that the beneficial wound healing outcomes were prolonged. (Karimi and Rockwell, 2019) Additionally, it was believed that the matrix would trap more leukocytes in its network, albeit this was difficult to demonstrate because slow centrifuge preparations might also have this impact. (He, Lin, 2009)

Another benefit of the fibrin clot's mass effect was stated that it could occupy space that PRP could not. (Kobayashi, Flückiger, 2016) Also, the scaffold was shown to allow peripherally growing cells to penetrate the injured area, which was not demonstrated to be achievable with the pure liquid PRP preparation. (Kobayashi, Flückiger, 2016) The scaffold character of PRF was particularly realistic because the fibrin clot was shown to be flexible and could be tailored to a variety of tissue defect forms. (Fan, Perez, 2020)

3. Types of PRF

In general, there are 2 forms of PRF: a solid form and a liquid form. (Fan, Perez, 2020) The solid PRF is the primary form of PRF prepared by Choukroun et al (Choukroun, Diss, 2006) in 2006. Its preparation without

anticoagulation, as was previously discussed, made it superior to PRP by creating a solid medium that could support a gradual release of growth factors. (Sunitha Raja and Munirathnam Naidu, 2008)

To separate the blood components in glass tubes, Choukroun et al (Choukroun, Diss, 2006) used a high centrifugal force (708 gravitational constant (g)) producing a dense PRF. The technique was later improved in 2018 by using a low centrifugal force (208g) and tubes made of plastic that were not as likely to activate a clotting cascade, thus producing what was called A-PRF. (Choukroun and Ghanaati, 2018)

A-PRF was assumed having a higher concentration of retained leukocytes because of its slower centrifuging and its more porous fibrin matrix, thus, a greater release of its contents was allowed. (Choukroun and Ghanaati, 2018, (Kobayashi, Flückiger, 2016) The greater porosity also was shown to allow for more blood vessel entry during angiogenesis. (Ghanaati, Herrera-Vizcaino, 2018) These malleable solid forms of PRF might be molded into pellets, divided into smaller pieces and mixed with bone grafts, or flattened and utilized as a membrane. (Kobayashi, Flückiger, 2016, (Movahedian Attar, Naghdi, 2017)

I-PRF was based on this slow centrifugal force principle by being prepared at 60g centrifuging force, i.e., at higher speed but for less time. (Mourão, Valiense, 2015) The outcome was a suspension like PRP but without anticoagulation, preserving the ability to form a slow release matrix when administered to tissues. (Agrawal, 2017, (Mourão, Valiense, 2015) This kind of PRF could be used to form sticky bone, which has a putty viscosity that could be easily handled, by mixing it with other graft materials like bone-grafting particles, in addition to injecting it into deep tissue spaces and open wounds. (Mourão, Valiense, 2015)

4. Applications of PRF in oral and maxillofacial surgery

4.1. PRF in implantology

A multitude of applications in implantology was proposed for PRF. (Ghanaati, Herrera-Vizcaino, 2018) As I-PRF, it could be mixed with bone grafts to confer maintained osteoinduction to the graft. (Del Corso, Mazor, 2012) As solid PRF, it could substitute the grafted bone entirely. (Fan, Perez, 2020) As malleable solid A-PRF, it could play a role as membranes that were proven helpful in GBR, maxillary sinus augmentation, and promoting healing in connective tissue grafting. (Ghanaati, Herrera-Vizcaino, 2018)

4.2. PRF in reconstructing bone defects

In 2002, Fennis et al (Fennis, Stoelinga, 2002) demonstrated that mandibular continuity defects could be reconstructed using platelet-concentrate scaffolds in animal models. Sohn's sticky bone, a blend of I-PRF and particulates graft, made it possible to handle and mold the bone graft with ease. (Gheno, Alves, 2022) The sticky bone was also highlighted to preserve much of its form during the healing process. (Fan, Perez, 2020) In addition, PRF could be introduced with or without a bone graft material as it was already reported as an osteoconductive scaffold by nature. (Fan, Perez, 2020)

After enucleation of cystic lesions of the jaws, PRF alone or in combination with autogenous or allogenous bone might be used to reconstruct considerable bony defects. (Dhote, Thosar, 2017) This could make sense as the objective after any large cystic lesion removal is to promote bone reformation. (Canellas, Medeiros, 2019) In many studies like the case report conducted in 2017 by Dhote et al (Dhote, Thosar, 2017), a successful treatment of radicular cyst in a 10-year-old patient related to a primary second molar using PRF was reported.

4.3. PRF in soft tissue grafting

In GBR, flattened solid PRF can be utilized as a membrane. (Miron and Choukroun, 2017) In addition, in 2018 Kuka et al (Kuka, Ipci, 2018) have demonstrated that the regenerative properties of PRF could also be utilized in conjunction with coronally advanced flaps for root coverage in multiple Miller class I (Miller, 1985) gingival recessions.

4.4. PRF in exodontia

Although allogenic, xenogeneic, and synthetic materials, as well as surgical methods using autogenous bone were widely used to decrease bone resorption, none of them was able to completely cease it. (Miron and Choukroun, 2017) PRF could enhance wound healing in the extraction socket and improve ridge preservation by introducing growth factors, angiogenic cytokines, and positive inflammatory cytokines. (Fan, Perez, 2020)

Studies have demonstrated that PRF enhanced the alveolar ridge preservation yielding less bone resorption. (Canellas, Medeiros, 2019) Moreover, the incidence of alveolar osteitis and postoperative pain after mandibular third molar extraction was reported low when PRF was placed in the extraction socket. (Al-Hamed, Tawfik, 2017, (Canellas, Medeiros, 2019)

4.5. PRF in oroantral communication (OAC) closure

PRF was assumed to offer an alternative option when used alone or combined with the techniques that were already in use; buccal advancement flap, buccal pad of fat, palatal pedicle flap, etc., for OAC closure. (Fan, Perez, 2020) In 2017, Assad et al (Assad, Bitar, 2017) reported an 8-week followed-up successful closure of 2 chronic OACs as a result of maxillary first molar extraction with 2 PRFs; 1 PRF clot was put inside the

extraction socket and then an additional PRF clot was flattened as a membrane and sutured to the gingiva. (Assad, Bitar, 2017)

In a modification to the 3-layer closure of OAC described by Weinstock et al (Weinstock, Nikoyan, 2014) in 2014, Verma and Verma (Verma and Verma, 2022) in 2022 utilized PRF to obtain a 4-layer closure of a chronic OAC. (Verma and Verma, 2022) In that latter technique, a press-refitted bony shelf, followed by coverage with buccal fat pad, PRF, then buccal mucosa, were involved to successfully close that chronic OAC. (Verma and Verma, 2022)

4.6. PRF in management of osteonecrosis of the jaw (ONJ)

The common objective of ONJ management was reported to achieve re-epithelization and vascularization of bone, as limited vascularization was a frequent association with ONJ. (Fan, Perez, 2020) In such situation, PRF was demonstrated possessing angiogenic properties that could promote angiogenesis. (Miron and Choukroun, 2017) Numerous studies have reported significant improvement in wound healing in medication-related osteonecrosis of the jaws (MRONJ) utilizing PRF. (Ghanaati, Herrera-Vizcaino, 2018) Re-epithelialization was also observed faster when PRF was used. (Ghanaati, Herrera-Vizcaino, 2018)

4.7. PRF in management of temporomandibular joint (TMJ) disorders

In 2020, Albilia et al (Albilia, Herrera-Vizcaíno, 2020) assumed that pain and dysfunction were decreased in patients with TMJ internal derangement receiving I-PRF injections. The involved patients in that study were classified with Wilkes classes I to V. (Wilkes, 1989) Two mL of I-PRF were injected for each TMJ; 1.5 mL into the superior joint space, and 0.5 mL into retrodiscal tissues. (Albilia, Herrera-Vizcaíno, 2020)

4.8. PRF in secondary alveolar cleft bone grafting (SABG

In 2016, Shawky and Seifeldin (Shawky and Seifeldin, 2016) assumed that in SABG, although PRF did not improve bone density, it was helpful in enhancing the newly formed bone volume when used in conjunction with iliac crest autogenous bone.

In the same context, in 2018, Natarajan and Rao (Natarajan and Rao, 2018) stated that PRF improved the gingival zenith when used with iliac crest bone grafts in SABG. In the same year, Omidkhoda et al (Omidkhoda, Jahnabin, 2018) investigated the efficacy of PRF combined with autogenous iliac crest bone graft in the quality and quantity of SABG. They concluded that the usage of PRF exerted no significant effect on the thickness, height, and density of maxillary alveolar graft. (Omidkhoda, Jahnabin, 2018) Similarly, Saruhan and Ertas (Saruhan and Ertas, 2018) in 2018 evaluated the significance of PRF in SABG when combined with iliac bone grafts, and claimed that no improvement was noticed in the newly formed bone.

In contrast, Desai et al (Desai, Kumar, 2019) in 2019 assumed that the use of PRF with iliac autogenous bone resulted in greater osteogenic effect which increased new bone regeneration and better wound healing. In another study in 2020, Francisco et al (Francisco, Fernandes, 2020) had reached a conclusion that PRF improved SABG as well.

Dayashankara Rao et al (Dayashankara Rao, Bhatnagar, 2021) in 2021 stated that the use of I-PRF and A-PRF with iliac bone grafts reduced the chances of bone resorption, showed higher percentage of bone volume and improved cleft's adjacent teeth periodontal health.

Likewise, Lavagen et al (Lavagen, Nokovitch, 2021) in 2021 investigated the efficiency of A-PRF usage in the treatment of alveolar cleft with iliac bone graft and concluded that A-PRF should be used routinely in SABG whenever possible.

Also in 2021, Al-Mahdi et al (Al-Mahdi, Abdulrahman, 2021) stated that PRF mixed with iliac crest autogenous bone graft significantly reduced postoperative bone resorption. As well, they claimed that PRF provided a higher bone density when evaluated six months later.

Interestingly, Aldaghir et al (Aldaghir, Naje, 2022) in 2022 hypothesized that maxillary cortical bone graft chips harvested by bone scraper and covered with PRF achieved a valid functional and aesthetic support in alveolar cleft patients, meeting the reconstructive goals.

As previously shown, PRF has been implemented in widely in the scope of oral and maxillofacial surgery. Further research is needed to probe the efficiency and practicality of PRF in this field.

Disclosure

The authors report no conflicts of interest in this work.

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