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Review Article

Use of Platelet-Rich Fibrin in Oral and Maxillofacial Surgery

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Abstract

Platelet-rich fibrin (PRF) is a strong but flexible fibrin including a enrich platelet which contain growth factors and cytokines. PRF can be made very simply and requires no artificial additives unlike platelet-rich plasma. While PRF is remodeled and released in the tissue, this induces cell growth, vascularization, collagen synthesis, osteoblast differentiation and an anti-inflammatory reaction. Taking advantage of these functions, PRF can stimulate regeneration of bone and soft tissue in a diverse number of ways during the course of hemostasis, wound coverage, preservation, and reconstruction of alveolar bone. Moreover, the use of PRF to improve bone regeneration has become a recent technique in implantology. In this study, through a literature review of PRF's existing clinical applications, we classified a range of potential PRF oral and maxillofacial surgery applications including preservation of extraction sockets, guided bone graft, sinus lift, dressing and periodontal treatment. This trial gave us chance to confirm the usefulness of PRF. Recently, updated clinical studies results concerning skin and tendon wound healing have become available. These results suggest that the usage of RPF will gradually expand.

Key words: Cytokines, Fibrin, Platelets

Introduction

Clinically, autogenous bones are considered an ideal bone graft material. Autogenous bones are capable of not only osteoconduction but also possess the capability for osteoinduction[1,2]. However, autogenous bone grafting creates many complications for the donor site and has limitation for harvesting. Allogenic bone, xenograft, and alloplastic bone have excellent qualities but do not have osteoinduction capability, and it is difficult to anticipate a good prognosis with the use of such types of bone in widespread alveolar augmentation or in treating bone defects with a small number of bony walls. Recently, in order to overcome these difficulties, there have been efforts made in using growth factors originating from the blood to increase bone formation[3,4].

Platelet-rich fibrin (PRF) was introduced by Choukroun *et al.*[5] and Choukroun *et al.*[6] PRF retains various growth factors and cytokines in a fibrin mesh structure, and during remodeling, it gradually releases cytokines[7]. Therefore, PRF supports not only hemostasis and wound healing but also immune responses. As it helps differentiate undifferentiated osteoblasts, PRF is used in various peripheral bone graft implant procedures, alveolar bone preservation,

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maxillary sinus bone grafts and other periodontal surgeries.

In this study, we will examine the theory and effects of PRF to identify its clinical applications in oral and maxillofacial surgery.

Theory and Use of Platelet-Rich Fibrin

1. History

PRF is a substance that was introduced to promote the healing response by using growth factors originating from the blood. It is a concentrated platelet that is obtained without any biochemical treatment. Tisseel (Baxter, Vienna, Austria) is the first tissue adhesive that was introduced. It had been used only for hemostasis because did not contain growth factors[8]. The material using the growth factor for the first time is platelet-rich plasma (PRP). PRP is formed artificially by adding a coagulant to blood, but has limitations: a requirement for two rounds of centrifugation and a short release time of growth factors[9].

PRF is a new generation of concentrated platelet that forms a flexible and strong fibrin mesh structure. As cytokine and growth factors gradually are release from PRF, it induces collagen synthesis and bone formation[10]. Because PRF is synthesized without any biochemical treatment of the source blood in simple method and releases growth factors for a longer period of time than PRP, it has attracted clinical attention and has been the focus of various studies[11].

2. Constitution of PRF to release of cytokines and growth factors

After blood is collected, it is centrifuged for 10 minutes at 3,000 rpm. This will separate the blood into an amorphous layer, a PRF layer in the middle, and a red blood cell layer on the bottom[12]. PRF goes through a gradual polymerization and forms a glycan chain within the fibrin mesh. Cytokines bind to this chain and mesh structure, locking in the platelets. PRF releases growth factors and can also function as a substrate for fibroblasts, blood vessels, and endotheliocytes[13].

Tuan *et al.*[14] reported about the role of fibrin in damaged tissue that fibroblasts recognize the fibrin structure, allowing the initiation of collagen synthesis. van Hinsbergh *et al.*[15] noted that blood vessel endotheliocytes can form a much wider range and more stable blood vessels in a polymerized fibrin structure. Dohan *et al.*[4] has emphasized that as this fibrin mesh structure is formed with three-dimensional and even trimolecular structure, it is a flexible and strong structure that can capture cytokines and moving cells.

When the fibrin mesh structure is remodeled, PRF releases cytokines connected to the glycan chain in its damaged structure. The types of cytokine released are as follows: interleukin (IL)-1β, IL-4, IL-6, tumor necrosis factor (TNF)-α, and vascular endothelial growth factor (VEGF). These cytokines mainly have anti-inflammatory and healing promotion roles. IL-1β, IL-6, and TNF-α are involved in anti-inflammatory activity and react to endotoxins and interferons. They are involved with the immigration and activation of blood vessel endotheliocytes and fibroblasts. In addition, they are involved in differentiation of lymphocytes, which, in turn, supports immunity responses. IL-4 and VEGF are involved in healing. They promote proliferation of lymphocytes and induce the immigration and proliferation of blood vessel endotheliocytes. They play a catalytic role in the generation of blood vessels[12,16].

The growth factors that are released from PRF are as follows: platelet-derived growth factor (PDGF), transforming growth factor (TGF)-β1, insulin-like growth factor (IGF), VEGF, and epidermal growth factor[17]. They are stored in an -granule of the platelets and facilitate signals within cells in damaged tissues and carry out roles such as cell growth, differentiation and collagen synthesis. When the function of the cytokines associated with PRF functions are examined collectively, PRF can be said to be involved in roles such as hemostasis, wound coverage, new inducement of blood vessel generation, support of immune responses, inducement of osteocyte differentiation inducement, and aiding the overall healing process[3,6,18].

Comparative studies on PRP and PRF are actively conducted. There are different opinions on PRF and its clinical effects, but in a comparative study on growth factors, Gassling *et al.*[16] argued that the concentration of cytokines that effect osteoblasts (PDGF, IGF, and TGF) is higher in PRP when compared to PRF. Also, the fibroblast-influences cytokine concentrations are far greater in

PRP, with the exception of TGF-β2.

However, Dohan and Choukroun[7] argued that due to a stable fibrin structure resulting from the polymerization process of PRF, the lifespan of PRF growth factors is longer than that observed in PRP, which was more than 7 days. Additionally, in a study by He *et al.*[19], the maximum release of TGF-β1 and PDGF from PRP is on the first day after the graft, while the maximum release from PRF is 7 and 14 days, respectively. The release of alkaline phosphatase reaches its peak on the first post-graft day in PRP but not until the 14th post-graft day with PRF. The He study also revealed that PRF can manifest a variety of growth factors that can promote differentiation and proliferation of osteoblasts. These results supported his opinion that PRF is superior to PRP in terms of release period.

3. Use of PRF in oral and maxillofacial surgery

When considering the PRF functions related to tissue regeneration, we can anticipate PRF 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, guided bone regeneration with/without implant, sinus lift (lateral, crestal approach), dressing agent and periodontic treatment.

4. Socket preservation

Choukroun *et al.*[6] indicated that when a PRF membrane is used, new blood vessels are generated and epithelialization is promoted. Consequently, this facilitates more rapid wound coverage. Also, after a cystic lesion is removed and filled with PRF, the time it takes it to be replaced naturally with new bone after 2.5 months. Similarly, Simon *et al.*[18], in their experiments with morphometric tissue in which they planned a socket preservation surgery using PRF, new bone was generated in only 3 weeks when a socket procedure was conducted using only PRF. However, it took 12 weeks to generate new bone in demineralized freeze-dried bone allograft (DFDBA) mixed with PRF group and DFDBA with barrier membrane group. Simon pointed out that inflammation and foreign body reaction caused slow bone formation in the group that used DFDBA, quoting a study by Becker *et al.*[20] and Becker *et al.*[21].

There are many reports, including a study by Shi *et al.*[22] and Shi *et al.*[23] that demonstrate significant rapid bone formation during the initial healing process when a platelet drug is used to perform socket preservation. Nevertheless, clinical research on the approximate width and height of alveolar bone PRF can maintain is insufficient. However, when socket preservation surgery is performed using PRF, the danger of exposure or complications decrease because a blocking membrane is not used, and there is decreased chance for a foreign body reaction and the associated decrease in bone substance.

5. Guided bone regeneration with and without implant

Studies on bone grafting using platelet drugs were conducted even before the studies on PRF. When grafted with fibrin adhesive and autogenous bone graft, the ratio of contact of the implant bone was 40.5%, which is higher than the 30.3% observed when only an autogenous bone graft takes place. Fibrin structure can promote bone formation on the graft[24]. He *et al.*[19] has reported, after experimenting with mice osteoblasts, that the growth factors of PRF can continuously induce the growth and differentiation of osteoblasts. When PRF is used on bone grafts, PRF are mostly used as a form of membrane. A barrier membrane could be added. Toffler *et al.*[25] have noted that if PRF is used as membrane, it prevents the leakage of bone graft material and quickens the regeneration of the gingiva. Kfir *et al.*[26] used alloplastic bone with PRF and barrier membrane. They reported that the width of alveolar bone that was formed was 1.3~3.9 mm while the possible vertical height was up to 2.4~5.1 mm.

In his 2009 study, Simonpieri *et al.*[27] demonstrated that a PRF membrane protects bone graft material and can increase gum maturity on maxillary alveolar bone grafting using autogenous bone, a 0.5% metronidazole solution and PRF membrane. Simonpieri *et al.*[28], in a clinical study of 184 cases with implants that was conducted in the same manner, also indicated that a PRF membrane can promote the healing and maturity of bone membrane, especially by increasing the thickness of gum around the implants. Over the 2.1-year period of his study, marginal bone absorption around the implants decreased significantly.

These results confirm that in alveolar grafting, PRF cannot replace bone graft materials, but it can play a role as a barrier membrane. Also, PRF can promote the healing of soft tissues such as periosteum and gingiva[6,18].

6. Sinus lift

The effects of PRF in treating maxillary sinus are remarkable. Choukroun *et al.*[5], in their research 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 histologic maturation of the test group after 4 months appears to be identical to that of the control group after a period of 8 months. Moreover, the quantities of newly formed bone were equivalent between the 2 protocols. When performing a maxillary sinus lift using PRF, there has been a report that indicates the healing period can be reduced by about 4 months. Also, in the same manner as observed in alveolar bone graft surgery, PRF can protect the maxillary sinus lateral window. To promote the healing of lateral gums, the lateral window can be covered by a PRF membrane[25,27].

Recently, a method was suggested where only PRF would be used in a maxillary sinus lift without any graft material[29]. Mazor *et al.*[30] used a lateral approach to lift the lower part of maxillary sinus, simultaneously placed an implant, and only placed PRF. Acquired bone height was 10.1±0.9 mm on average, and they reported that there were no implant failures. Inside the maxillary sinus, PRF not only prevents damage to the maxillary sinus membrane, it also promotes bone formation and can help maintain the height of the lifted maxillary sinus for a certain period of time (Fig. 1, 2).

In experiments conducted by Choi *et al.*[31], the maxillary sinus membrane was intentionally perforated about 2 mm, received fibrin glue and collagen membrane, and was histologically analyzed. The maxillary sinus membrane was restored to a continuous structure as before in fibrin glue group, but inflammation and infiltration of fibrotic tissues were observed in collagen membrane group. When we examine the study in which the maxillary sinus membrane is perforated more than 2 mm, the results indicate that for bone graft material, a dome shape falls apart and graft material leaks into maxillary sinus. PRF, on the other hand, is anticipated to prevent leakage of the bone graft material and can induce rapid healing when the maxillary sinus is perforated.

PRF is effective for maxillary sinus lift through the alveolar crest (osteotome-mediated sinus floor elevation [OMSFE]) in that it can reduce the damage in the maxillary membrane. In a clinical experiment by Toffler *et al.*[32], and Toffler[33], when lifting was conducted using the OMSFE technique and only PRF, the height of implant sites was an average of 3.4 mm, and the time it took to connect the sites to the abutment post was about 4 months. When residual alveolar bone is 5~8 mm, OMSFE is an advantageous surgery technique. Diss *et al.*[34] also claimed that when PRF is used by itself in an OMSFE-based surgery, the healing period can be reduced to 2~3 months until the implant

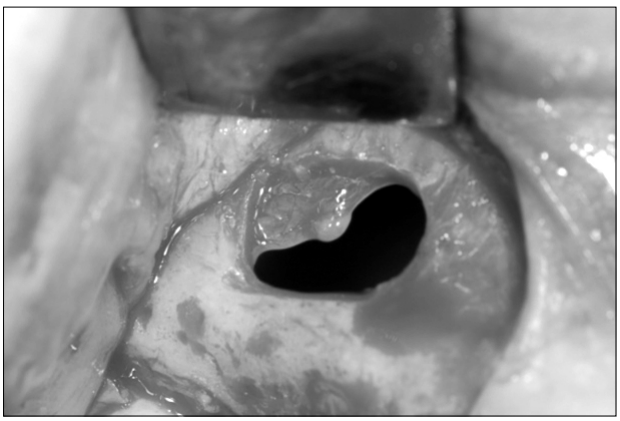

Fig. 1. Sinus membrane that was perforated during sinus elevation via lateral approach.

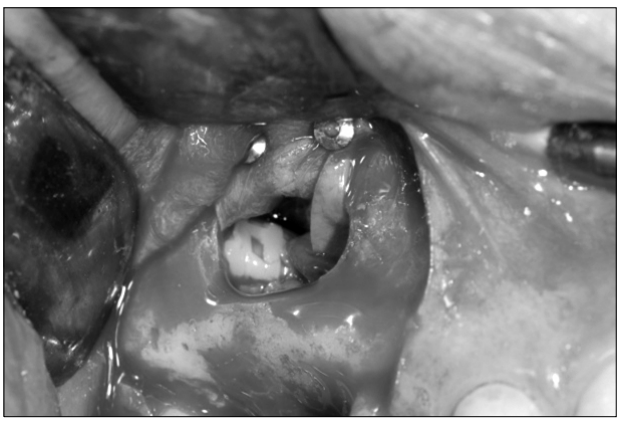

Fig. 2. Sinus membrane that was perforated was covered by BioGide (Geistlich Pharma AG, Wolhusen, Switzerland) and elevated using platelet-rich fibrin.

can handle 25 Ncm, and an average of 3.2 mm of new bone is formed. The biggest problem when approaching the maxillary sinus through the alveolar ridge is that it is difficult to verify perforations. There has been a report that indicates perforation in the maxillary sinus membrane is observed in about 30% of surgeries. Diss, when discussing the advantages of using PRF in the OMSFE technique, noted that as the osteotome does not have direct contact with the maxillary sinus, the danger of perforation can be reduced, and due to the fibrin structure, the risk of perforation after the surgery is reduced. In addition, PRF can prevent leakage of the bone materials into the maxillary sinus.

7. 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[11,28]. Sammartino noted that in heart disease patients who take anticoagulant drugs, PRF was used to filled in the socket after a dental extraction without discontinuing the drugs[35]. Such patients can anticipate hemostatic effects, reduced pain after extraction and prevention of dry socket. According to a study by Toffler[33], when PRP was used in the sockets of the test group, the test group experienced at least four times lower occurrence of dry socket compared to the control group. Simon *et al.*[18] also recommend PRF filling in sockets as it can help rapidly form bone and cover the wounds.

Also, due to the enhancement of quality and thickness of the periosteum and gingiva, in addition to the bone regeneration ability, PRF is useful in regenerating periodontal tissue around implants[6,28,36]. In You *et al.*[37]'s study examining tissues around implants that were intentionally infected and subsequently treated with autogenous bone and fibrin glue to facilitate healing, the group that used fibrin glue obtained a bone-to-implant contact of 50.1±14.1, which was significantly different from autobone graft group (19.3±8.1) or the non-graft control group (6.5±7.5). Fibrin glue, especially, was said to be useful in re-osseointegration of implants.

8. Periodontic treatment

Irrespective of implants, the effects of PRF on periodontal tissue regeneration are also receiving attention. PRF is known to induce differentiation and proliferation of fibroblasts, and it can induce the fundamental regeneration of periodontal tissues[6,7,16].

Sharma and Pradeep[38] reported that defect of bifurcation was improved with PRF and PRF can be an outstanding material in treating defect of bifurcation. Aroca *et al.*[36] performed modified coronally advanced flap surgery with PRF to cover exposure root. The degree of coverage and thickness of gingival were significantly higher in PRF group than the control group which did not use PRF. In addition, 6 months later, 74.6% of the PRF group completely presented coverage. However, Aroca *et al.*[36] revealed that no difference between probing depths were observed, suggesting that this technique with PRF can fundamentally regenerate periodontal tissues.

Conclusion

Although PRF has not been studied for a long time, it can be utilized usefully in oral and maxillofacial area; it is biocompatible and can induce fundamental regeneration of bone and soft tissue. Especially as used in this study, PRF can produce outstanding results in socket preservation surgery, alveolar and maxillary sinus bone graft, procedures to reduce inflammation around implants and periodontal surgeries. If more clinical studies are carried out, PRF might establish itself as a treatment of good prognosis. Also, in recent reports, the effective treatment of skin and tendon wounds have been demonstrated[39,40]. The practical use of PRF will expand in oral and maxillofacial treatments and other areas.

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