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Application of Platelet-Rich Fibrin (PRF) in Oral and Maxillofacial Autologous Fat Transplantation

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Abstract

Due to its various advantages, including minimal invasiveness, high safety and sufficient availability, autologous fat transplantation has been widely used in the repair of soft tissue defects in the oral and maxillofacial regions; however, its high postoperative fat absorption rate remains a major problem for clinicians. In recent years, it has been found that the high levels of growth factors and dense three-dimensional network structure in Platelet-Rich Fibrin (PRF) provide a suitable microenvironment for the growth of fat in transplantation areas, which can promote the adhesion and proliferation of adipose-derived stem cells. PRF is an ideal material to solve the problem of a high fat absorption rate. This article reviews the efforts of clinicians to reduce the absorption rate of fat transplantation, analyzes the effect of PRF on adipose stem cells, summarizes the clinical application of PRF in oral and maxillofacial fat transplantation, and preliminarily summarizes and discusses some problems existing in PRF in oral and maxillofacial fat transplantation. The hope is that PRF will be more widely used in oral and maxillofacial fat transplantation.

Keywords: Autologous fat transplantation; Platelet-rich fibrin; Oral and maxillofacial

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The High Absorption Rate of Transplanted Fat is a Clinical Problem to be Solved

In 1893, Dr. Neuber first reported the extraction of arm fat to repair facial soft tissue deformity, confirming that fat transplantation can be used to restore the facial shape and improve scarring [1]. Since then, an increasing number of doctors have begun to apply fat transplantation in the treatment of soft tissue defects for various reasons and have achieved good results. However, since the invention of fat transplantation technology, clinicians have encountered the problem of fat absorption in the transplantation area. In different reports, the fat absorption rate in the transplantation area is 20% to 90% [2]. Therefore, scholars began to reduce the fat absorption rate by improving fat transplantation technology.

In 1909, Dr. Holländer first tried to improve the injection device, that is, by using a cannula to inject fat [3]. In the 1980s, Pierre Fournier and Yves Gerard Illouz first tried to improve the method of fat extraction [4,5]. Pierre used a small injector to pump fat considering the trauma to the donor site, while Illouz used a negative-pressure pump to pump fat on this basis. This improvement *via* negative-pressure liposuction reduced the fat absorption rate and the incidence of complications to a certain extent. In the 1990s, Sydney R. Coleman first proposed a standardized process of fat transplantation, which is still widely used today. It is called the Coleman technique and is based on the following principles: Low negative-pressure blunt-needle liposuction; centrifugal purification and classified treatment of fat; and blunt-needle, multilevel, multitunnel uniform microinjection [6]. The emergence of the Coleman technique was of great significance for the promotion of fat transplantation technology worldwide. Although improvements in technology have reduced the fat absorption rate to a certain extent, multiple transplantation and filling procedures are still necessary to achieve the desired effect, which increases the burden on both doctors and patients. In recent years, with the development of autologous tissue engineering, scholars have tried to further reduce the fat absorption rate by applying tissue engineering strategies in transplantation areas, that is, adding seed cells, growth factors or constructed scaffolds.

In 2006, Yoshimura proposed Cell-Assisted Lipotransfer (CAL) technology [7], that is, extracting Adipose-Derived Stem Cells (ADSCs) in the process of fat transplantation and then adding them into fat, which effectively reduced the fat absorption rate. In 2012, Butala found that adding endothelial progenitor cells to fat can improve the formation of fat microvessels in the transplantation area, which is conducive to the survival of fat in the transplantation area [8]. In addition to seed cells, in recent years, scholars have found growth factors, such as Platelet-Rich Fibrin (PRF), a second-generation platelet concentrate derived from autologous blood, has the advantages of simple preparation, wide availability and high safety and is thus an ideal material for clinical tissue engineering in fat transplantation areas [9].

PRF is an Autogenous Material that is Expected to Reduce Fat Absorption after Transplantation

PRF was first reported by the French scholar Choukroun in 2000. Because of its dense solid structure, PRF was distinguished from the first generation of platelet concentrate-Platelet-Rich Plasma (PRP). The method for preparing PRF is different from that for preparing PRP; that is, without adding biological enzymes, 10 ml of venous blood is immediately added into the centrifuge tube and centrifuged at 3000 r/min for 10 min [9]. After removing the centrifuge tube, the blood layer was observed. The top layer is the Pale-Yellow Platelet Plasma (PPP) layer, the middle layer is the required PRF layer, and the bottom layer is the red blood cell layer (Figure 1A, 1B). After the middle layer of PRF gel was cut, the liquid portion was removed by rapid extrusion with two sterile pieces of gauze to prepare the PRF film, i.e., the final product (Figure 1C). After the PRF membrane is obtained, it can be cut up and used directly for filling or as a direct cover due to its plasticity (Figure 1D). In fat transplantation, we usually cut PRF gel directly and mixed it with fat. To discover its biological function, scholars began to analyze the structure and composition of PRF.

PRF is Beneficial to ADSC Adhesion and Proliferation

Structural analysis of PRF has shown that the biomaterial is composed of cytokines, sugar chains and structural glycoproteins tightly combined in a fibrous network. It has a very dense three-dimensional network structure that is similar to the structure resulting from natural polymerization during overprocessing by centrifugation; which structure is even more uniform and dense than that of the natural structure [10]. The structure of PRF is conducive to the chemotaxis and adhesion of various growth factors, inflammatory factors, and surrounding cells, as well as the storage of oxygen and nutrients. The dense three-dimensional structure provides sufficient mechanical strength and plays a protective role in the adhesion of cells and growth factors to a certain extent.

Component analysis of PRF has shown that PRF releases a large number of growth factors, such as Endothelial Growth Factor (VEGF), Insulin-Like Growth Factor (IGF), basic Fibroblast Growth Factor (bFGF), Transforming Growth Factor (TGF)-β1, Platelet-Derived Growth Factor (PDGF-AB) and Epidermal Growth Factor (EGF), which can promote cell growth and promote wound healing [10]. Some scholars have performed comparative experiments between PRP and PRF *in vitro* and found that PRF can release a large number of growth factors more continuously than PRP, lasting for 1 week to 28 days [11]. Additionally, it was found that the slow blood activation process of PRF could induce an increase in leukocyte

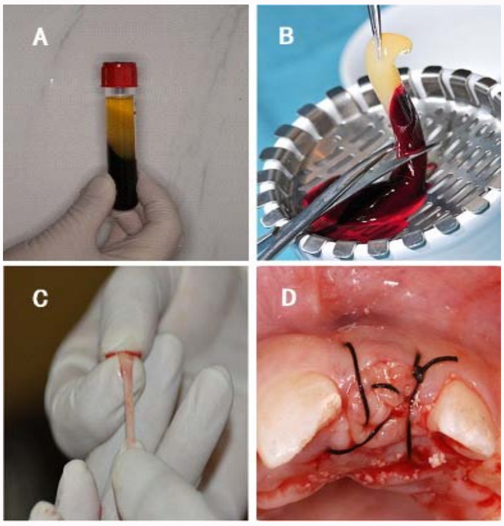

Figure 1: Production and use of PRF. A. View after venous blood centrifugation. B. Separation of the PRF layer and red blood cell layer. C. Collection of the PRF membrane. D. Placement of PRF in a wound.

degranulation [12], indicating that PRF also has a strong immune defense effect. Leukocytes in PRF can also secrete inflammatory factors. Some scholars measured the levels of three proinflammatory cytokines (IL-1B, IL-6 and TNF-α), one anti-inflammatory cytokine (IL-4) and VEGF and found that the levels of IL-1B, IL-6, IL-4 and TNF-α were significantly increased. However, whether the dense three-dimensional network structure and large number of growth factors of PRF are needed for fat transplantation remains unclear.

Yoshimura's theory on transplanted fat survival 6 suggests that the granular fat tissue in the transplantation area is supplied by interstitial fluid and not blood in the early stage, resulting in only mature grafted adipocytes surviving in the outermost survival area (<300 μm) and fat stem cells and fat precursor cells that can withstand ischemia and hypoxia surviving in the intermediate regeneration area. Moreover, no cells in the central necrotic area of the graft survive, which indicates that a microcirculation blood supply should be established early in the transplantation area. This is the key to providing sufficient nutrition for the cells and improving the survival rate of transplanted fat. A large amount of nutrients is stored in the dense structure of PRF, and it has slow-release characteristics; therefore, PRF can provide sufficient nutrition and space for the adhesion, proliferation and differentiation of fat stem cells and fat precursor cells. In our study, we extracted PRF and ADSCs and used a pure PRF membrane as the control. The adhesion of ADSCs on the PRF membrane was observed at three time points, namely 3 days, 7 days and 21 days, by Electron Microscopy (SEM) at magnifications of x500, x1000 and x5000 (Figure 2). The ADSCs gradually spread over time, occupying the entire surface of the PRF membrane at 21 days. These results suggest that the dense three-dimensional structure of PRF may promote ADSC adhesion.

Furthermore, it has been speculated that PRF continuously promotes angiogenesis and blood supply reconstruction in the transplantation area under the action of many angiogenic cytokines, such as PDGF and VEGF. Some studies have shown that IGF can upregulate lipid-related signaling to promote the adipogenic differentiation of fat precursor cells and that PDGF can significantly improve the survival and differentiation ability of fat precursor cells

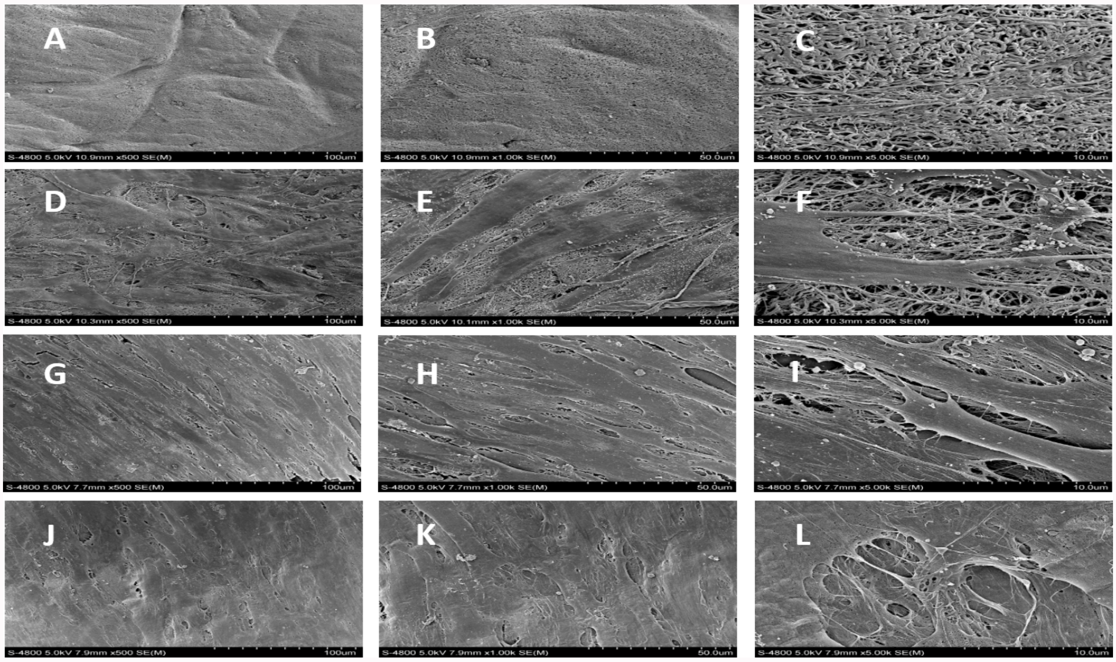

Figure 2: ADSC morphology and status after co-culture with PRF.
A. PRF under SEM (x500). B. PRF under SEM (x1000). C. PRF under SEM (x5000). D. ADSCs with PRF under SEM after 3 days (x500). E. ADSCs with PRF under SEM after 3 days (x1000). F. ADSCs with PRF under SEM after 3 days (x5000). G. ADSCs with PRF under SEM after 7 days (x500). H. ADSCs with PRF under SEM after 7 days (x1000). I. ADSCs with PRF under SEM after 7 days (x5000). J. ADSCs with PRF under SEM after 21 days (x500). K. ADSCs with PRF under SEM after 21 days (x1000). L. ADSCs with PRF under SEM after 21 days (x5000).

[10]. Some scholars further studied the proliferation of ADSCs in medium supplemented with 1/10, 2/10 and 3/10 PRF (extruded PRF liquid was mixed with culture medium in different proportions) and found that PRF had concentration- and time-dependent effects on the proliferation of ADSCs [2]. These results suggest that PRF is beneficial for the proliferation of ADSCs. We repeated the above experiments and added low concentrations of PRF, namely 1/100, 1/200 and 1/1000, to observe the proliferation of ADSCs at 1 to 6 days (Figure 3). The CCK-8 assay results showed results consistent with the above conclusions in the 1/10, 2/10 and 3/10 groups. In the low concentration group, on the third day, the proliferation rates of the 1/100, 1/200 and 1/1000 groups were slightly higher than that of the control group; there were no significant differences between these groups and the control group at any other time point. Thus, we found that the proliferation of ADSCs is positively correlated with the concentration and duration of PRF exposure. The higher the concentration is, the more significant the effect; that is, PRF can significantly promote the proliferation of ADSCs.

Based on the above results, PRF may reduce the fat absorption rate of transplantation because of its dense three-dimensional structure and large number of growth factors.

PRF-Assisted Fat Transplantation Can Effectively Reduce the Fat Absorption Rate

After obtaining good cytological results, scholars began to further establish animal models. Some scholars established a nude mouse fat transplantation model in which a total of 24 mice were randomly divided into the PRF group and the control group, and samples were collected at 1, 2, 3 and 4 weeks for analysis [13]. The results showed that the volume and weight retention rates were higher in the PRF group, the expression levels of various factors promoting fat formation were higher, the expression levels of various factors inhibiting fat formation were lower, the vascular density was higher, the degree of fibrosis was lower, and the survival rate was higher. The conclusion was that PRF can promote the autocrine function of transplanted fat, produce more growth factors, and improve the survival rate of fat by promoting vascularization and adipogenic differentiation, inhibiting apoptosis and regulating the production of collagen. Some scholars further studied and compared the effect of PRF and PRP on fat transplantation. The groin fat pad of rabbits was processed into granular fat. The fat was treated with PRF in one group and PRP in another group and then transplanted into the back of one ear. After 12 weeks, the fat survival rate and neovascularization capillary density in the PRF group were significantly higher than those in the PRP group, and both groups showed values higher than those in the blank control group [14]. To date, in different animal model studies, PRF has been found to be an ideal material for effectively reducing the fat absorption rate, but animal experiments alone cannot fully prove the safety and efficacy of PRF for clinical use; thus, scholars began further clinical trials for confirmation.

Clinical Application of PRF-Assisted Fat Transplantation

The complete process of oral and maxillofacial autologous fat transplantation is divided into three parts: Adipose tissue acquisition, treatment and injection [15]. Clinically, to minimize trauma to the patient and increase the convenience of the operation, we often choose the abdomen or the inner thigh as the donor site. Because PRF is easy to prepare, the process of PRF preparation and mixing PRF with fat is often considered the treatment of adipose tissue. PRF is obtained by the Choukroun method while fat is prepared. Then, the PRF was cut into fragments less than 1 mm in diameter, and the fat was mixed with PRF and transferred into a 1 ml syringe.

Zhang et al. [16] compared the postoperative satisfaction rate of

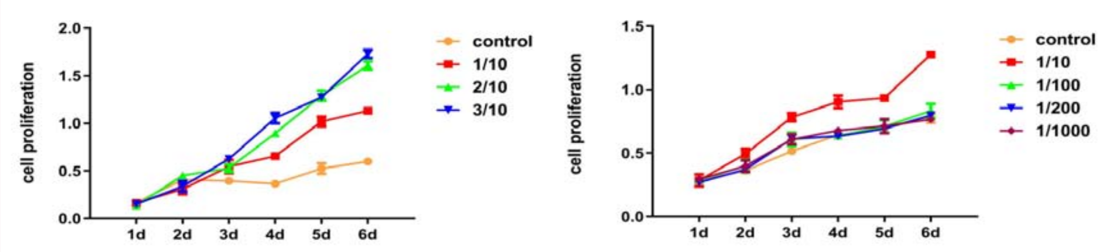

Figure 3: Proliferation ADSCs cultured with PRF assessed by CCK-8 assay. Proliferation of ADSCs after culture with PRF at different concentrations. From the third day of the study, at each time point, the absorbance was higher in the 1/10, 2/10 and 3/10 PRF groups than in the control group, showing a trend of increasing absorbance with increasing concentration, while there was no significant difference in absorbance between the control and 1/100, 1/200 and 1/1000 PRF groups.

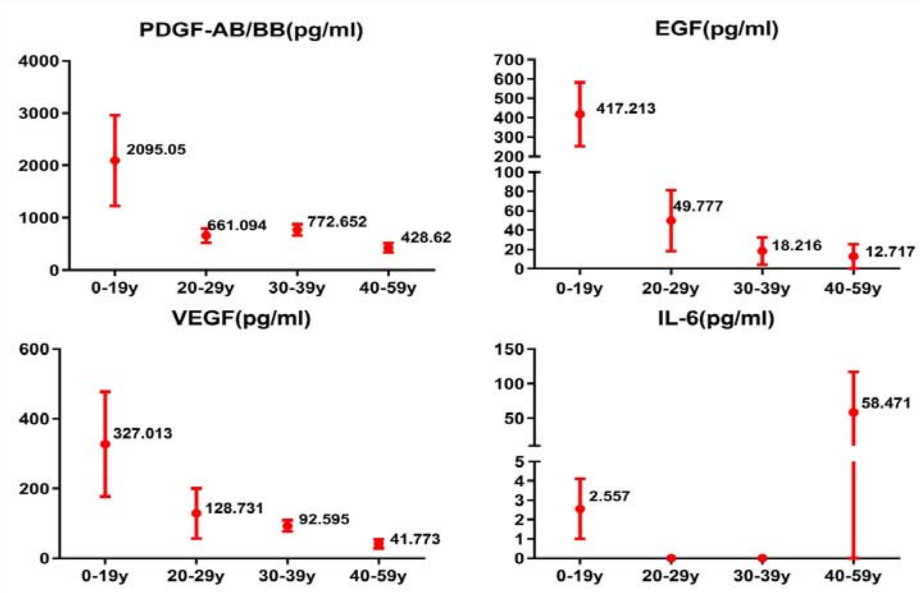

Figure 4: Molecular content of PRF in different age groups. There were 5 patients in the 0 to 19 age group, 5 patients in the 20 to 29 age group, 6 patients in the 30 to 39 age group, and 3 patients in the 40 to 59 age group. The levels of PDGF-AB, VEGF and EGF decreased with increasing age, and IL-6 was only found in the 0 to 19 and 40 to 59 age groups.

300 patients after PRF-assisted fat transplantation and traditional fat transplantation in the oral and maxillofacial regions was compared, including 68 patients in the PRF group and 232 patients in the conventional group. Compared with the conventional group, the PRF group showed a higher patient satisfaction rate, fewer postoperative refilling procedures, better skin texture and fewer complications. These results show that the application of PRF in oral and maxillofacial autologous fat transplantation in the clinic can not only effectively reduce the fat absorption rate but also reduce postoperative pain and complications, which suggests that PRF-assisted fat transplantation is safe, effective and feasible. Keyhan et al. [17] compared the effect of PRF and PRP in buccal and zygomatic fat transplantation. A total of 25 patients (8 males and 17 females) were treated with PRP on one side and PRF on the other side. According to the statistics, one year after the operation, the fat survival rate was higher and the facial aesthetics were better on the PRF side, indicating that PRF combined with fat transplantation is more effective than PRP combined with fat transplantation. To date, clinical trials have proven that PRF-assisted fat transplantation is safe, effective and feasible in facial fat transplantation. In addition, some scholars have further studied the role of PRF-assisted fat transplantation in rhinoplasty. Milos Kovacevic et al. [18] studied 107 patients (72 females, 35 males) with PRF combined with large granular fat (30 mm × 15 mm ×1.5 mm to 22 mm) in rhinoplasty were followed up for an average of 14 months. The results showed that the skin quality of all patients was good, there were no signs of contraction, obvious scars or color changes, and the patient satisfaction was good. Ultrasound and magnetic resonance imaging confirmed fat survival, which proved that large granular fat transfer combined with PRF to the back of the nose is a safe and feasible method. Dan et al. [19] further compared the role of PRF combined with high-density fat and conventional fat transplantation in rhinoplasty. Seventy patients were randomly divided into the PRF combined with high-density fat transplantation group (combined group) and the conventional fat granule transplantation group (control group). The patients were followed up for more than one year. The results showed that the success rate of one operation was higher in the combined group, and only one case needed two operations. An average increase in nasal height, a more stable nasal shape and higher patient satisfaction were observed in the combined group 6 months after the operation. The authors said that PRF combined with autologous high-density fat transplantation is simple, the fat retention rate is significantly improved compared with the control group, and the long-term curative effect is stable without obvious adverse reactions. It is recommended that this method be widely used in clinical augmentation rhinoplasty. Milos Kovacevic and Dan [18,19] selected different sizes of fat in rhinoplasty and

played a better role after mixing PRF, indicating the effectiveness of PRF in different sizes of fat. In clinical work, in addition to large fat and granular fat, more fine fat should also be selected for patients who need facial micro filling.

In recent years, the emergence of nanofat has provided a new method of obtaining material for fine injection. Fat can be emulsified to obtain smaller particles of chylous fat, which is more conducive to microfilling of the face and further broadens the indications for fat transplantation. PRF is known to promote the survival rate of transplanted fat, and scholars have begun to explore the effect of PRF-assisted nanofat in oral and maxillofacial autologous fat transplantation. Some scholars compared the effect in 62 cases of transplantation of PRF combined with nanofat and 77 cases of traditional fat transplantation in the oral and maxillofacial regions by comprehensively evaluating differences in the facial contour, skin texture, complications and satisfaction of all patients before and after treatment by subjective and objective tripartite assessments [2]. The results showed that patients in the PRF group had a higher satisfaction rate, fewer complications, and more obvious improvement in facial contour and skin texture. The conclusion was that PRF is also suitable for assisting nanofat in oral and maxillofacial autologous fat transplantation. This suggests that PRF has a similar effect when combined with different forms of fat and that there is no form of fat that is superior in PRF-assisted fat transplantation in the clinic. Therefore, the best fat transplantation scheme should be selected according to the actual situation of the patient. PRF has become rapidly popular in the field of fat transplantation because of its advantages of being simple to prepare, extensively available, safe and effective. PRF-assisted fat transplantation has gradually become a conventional method of autologous fat transplantation.

Looking Forward

Due to the advantages of the simple preparation, safety and efficacy of PRF, it was applied in the clinic shortly after being reported. Although it effectively reduced the fat absorption rate, the average fat absorption rate after transplantation was still as high as 40% [14], and one operation could not meet the needs of most patients. Therefore, on the one hand, some scholars have aimed to improve PRF and produce many derivatives of PRF; on the other hand, some scholars have conducted more detailed research on the clinical application of PRF-assisted fat transplantation.

Do PRF derivatives perform better in fat transplantation?

After PRF, people gradually realized that a dense structure and growth factors are key to reducing fat absorption. In 2006, Sacco further prepared Concentrated Growth Factors (CGFs) from venous blood [20]. Compared with PRF, CGF has greater structural strength and more growth factors. The only difference from PRF is that CGF requires a specific centrifuge for preparation by variable-speed centrifugation. It has been reported that compared with PRF, CGF contains higher levels of growth factors and has a stronger effect on the proliferation of ADSCs [21]. Some scholars have established animal models to compare the effects of CGF, PRF and PRP in fat transplantation. The results showed that the weight and volume of fat grafts in the CGF group were higher than those in the other groups [21]. Histology showed a higher vascular density and fewer complications in the CGF group. Although the efficacy of CGF has been confirmed in animal models, whether a denser structure will adversely affect the transplantation site of patients in the clinic remains to be determined.

Considering that membranous PRF is not suitable for injection in facial microfilling, some scholars have made an injectable form of PRF, which is different from the previous PRF membrane and is called I-PRF [22]. In one study, 32 patients were treated with I-PRF and autologous fat transplantation for upper eyelid depression correction [23]. Satisfactory results were achieved, and I-PRF was more suitable for auxiliary fat microfilling.

Although basic research and animal experiments have shown that PRF derivatives have broader prospects for application in fat transplantation, both CGF and I-PRF are made on the basis of PRF, and there is no significant alteration. However, their clinical indications and adverse reactions still need to be further studied.

Is there an optimal age for PRF extraction?

PRF is an autogenous platelet concentrate. Growth factors such as PDGF-AB, VEGF, and EGF promote cell growth and are conducive to wound healing, and inflammatory factors such as IL-6 promote the inflammatory response and are not conducive to wound healing. Will the content of these growth factors change with patient age? Our team extracted PRF samples from 19 patients aged 0 to 19, 20 to 29, 30 to 39 and 40 to 59 years and compared the levels of four growth factors, i.e., PDGF-AB, VEGF, EGF and IL-6 (Figure 4). We found that the levels of PDGF-AB, VEGF and EGF decreased with increasing patient age. There was no significant difference in the PDGF-AB level between the 20 to 29 and 30 to 39 age groups, no IL-6 was found in the 20 to 29 and 30 to 39 age groups, and the level of IL-6 was much lower in the 0 to 19 age group than in the 40 to 59 age group. In conclusion, the levels of PDGF-AB, VEGF and EGF in the 0 to 19 age group were much higher than those in the other groups, while the level of IL-6 was lower, indicating that 0 to 19 is the best age range for the extraction of PRF. Overall, we inferred that the younger the patient was, the better the overall results of PRF extraction.

What is the best mixing ratio of PRF to transplanted fat?

In clinical work, different doctors use different mixing ratios of PRF to fat. Although different reports have shown that PRF can reduce the fat absorption rate, the reported results are not comparable among the studies. Therefore, some scholars established animal models and conducted research on the mixing of PRF with fat according to volume ratios of 1:5, 1:10, 1:15 and 1:20. The results showed that the volume and mass retention rates were significantly higher in the 1:5, 1:10 and 1:15 groups than in the 1:20 group and the control group. Evaluation of the blood vessel count, and viable adipocyte count showed better results in the 1:5, 1:10 and 1:15 groups than in the other groups [24]. The authors conclude that the volume ratio of PRF to fat 1:10 is the best ratio for clinical application, which is consistent with our clinical experience (oral and maxillofacial autologous fat transplantation volume less than 60 ml).

Is the effect of PRF combined with ADSCs better?

In recent years, since PRF has become increasingly popular in the field of fat transplantation, some scholars, based on the concept of tissue engineering, have added ADSCs as seed cells on the basis of the dense three-dimensional structure and large number of growth factors of PRF to achieve better results. Some scholars used human fat granules and venous blood to prepare PRF and ADSCs and then created four groups: The PRF combined with ADSC group, the ADSC group, the PRF group, and the control group. Mixed human fat granules were implanted into subcutaneous cavities on both sides of the backs of nude mice. The effect of PRF combined with ADSCs was the best in terms of the microvessel density, fat survival rate, and incidence of complications [25]. However, the process for preparing ADSCs is complex and involves expansion and culture in the laboratory, so this method is not suitable for clinical application. Therefore, some scholars further improved the extraction method to obtain a multicellular component, i.e., Stromal Vascular Fraction (SVF), which is an adipose-derived multicellular mixture dominated by ADSCs.

Several studies have confirmed that the auxiliary use of SVF and PRF can reduce the absorption rate of transplanted fat and improve the overall effect of fat in plastic surgery. First, a small-animal study was carried out with the rabbit auricle as the test carrier 26 in five groups: Traditional fat transplantation, SVF-assisted fat transplantation, SVF combined with PRP-assisted fat transplantation (without activator), SVF combined with PRP-assisted fat transplantation (activator) and SVF combined with PRF-assisted fat transplantation. The results showed that PRF combined with SVF had the lowest fat absorption rate and the best effect, with an average long-term absorption rate of only 18%. Second, histological and immunohistochemical observations showed that the combination of SVF and PRF was superior to the other treatments in terms of the fat graft absorption rate and microvascular reconstruction ability. In a follow-up large-animal study, a pig model of fat transplantation was established [27]. The model proved that the advantages of the combined application of PRF and SVF were obviously reflected in different models and different regions, suggesting the feasibility of human clinical application; however, there have been no clinical studies.

At present, although there have been no reports on the combined application of PRF and SVF in the clinic, the combined application of PRP and SVF has become increasingly mature. It has been reported that the combined application of PRP and SVF is effective and feasible in fat transplantation-related operations, such as facial rejuvenation plastic surgery and breast augmentation surgery [28]. Based on the clinical reports of PRP combined with SVF in fat transplantation and the comparison of the above animal experiments, we believe that PRF combined with SVF is more effective and has broader prospects. Our research group has applied it in the clinic for comparison with other fat transplantation techniques, and the effects will be reported in the future.

Patient Consent and Ethics Approval

This study was approved by the medical ethics committee of the Stomatological Hospital of the Fourth Military Medical University (IRB-REV-2018036). From April 3rd, 2021, to April 28th, 2021, all patients in this study provided blood for PRF collection at the Department of Plastic Surgery, Stomatology Hospital of the Fourth Military Medical University. There were 19 patients aged 7 to 52 years; 13 patients were men, and 6 were women. All patients signed informed consent forms.

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