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Review

Platelet-rich fibrin in plastic surgery

QM Zhao[1]*, YJ Ding[1], T Si[1]

Abstract

Introduction

Platelet concentrate has been used in surgery for many years. The initial concept of these autologous preparations was to concentrate platelets and their growth factors and to deliver it to a surgical site, in order to improve local healing. Platelet-rich fibrin (PRF) is the new generation of platelet concentrate. Choukroun's PRF (L-PRF) is the latest development of platelet concentrate protocols, which was first developed in France by Choukroun et al. in 2001 as an autologous biomaterial.

PRF is obtained centrifugally by autologous peripheral blood, without adding any biological agents. PRF contains the fibrin matrix polymer, leucocytes, cytokines and circulating stem cells. PRF could be classified into two categories, depending on their leucocyte content: pure platelet-rich fibrin (P-PRF) and leucocyte- and PRF (L-PRF).

PRF is produced with a simple method, it is low cost and easily available, which has been applied in many different fields, particularly oral and maxillofacial, orthopaedic and plastic surgery. L-PRF and PRFM (P-PRF) are both applied in plastic surgery and the applications can be divided into two aspects: facial plastic surgery and wound healing. The aim of this review was to discuss platelet-rich fibrin in plastic surgery.

Conclusion

Unfortunately, this field of research suffered from some problems for many years, such as the lack of a coincident terminology and the leucocyte content. Further studies are necessary to validate the interest of the PRF in plastic surgery.

This review describes the classification, preparation, applications and problems of PRF in plastic surgery.

* Corresponding author
Email: zhaoqmzx@yahoo.com.cn

[1] Department of Plastic and Reconstructive Surgery, PLA Hospital of No.117, Hangzhou

Introduction

The recent development of platelet concentrate for surgical use is an evolution of the fibrin glue technologies used for many years. The initial concept of these autologous preparations was to concentrate platelets and their growth factors in a plasma solution, and to activate it into a fibrin gel on a surgical site, in order to improve local healing. Platelet-rich fibrin (PRF) is the new generation of platelet agglutination, which was first developed in France by Choukroun et al. in 2001 as an autologous biomaterial[1]. PRF contains a fibrin matrix polymer, blood aggregates, leucocytes and cytokines as well as the involvement of circulating stem cells. PRF is obtained centrifugally by autologous peripheral blood, without adding any biological agents. PRF is produced with a simple method, it is low in cost and easily available, which has been applied in many different clinical fields, particularly oral and maxillofacial surgery, orthopaedics, as well as plastic surgery.

This review describes the classification, preparation, applications and problems of PRF in plastic surgery.

Discussion

The role of platelets

Platelets are small pieces (2-3 μm in diameter) of a nucleate cytoplasm with biological activity, which are from the mature megakaryocyte cytoplasm lysis and shedding in marrow. They contain many granules, few mitochondria and two prominent membrane structures, the surface connected canalicular system and the dense tubular system. Activation of platelets is mediated by contact with the site of injury and attachment to the fibrin scaffolding formed at the site of injury. Fibrinogen is activated immediately after trauma by platelets to form into the fibrin clot that play an important role in haemostasis[1]. However, it is known that platelets play a crucial role not only in haemostasis, but also in the wound healing process[2]. Platelets release a variety of cytokines and growth factors, including tumour growth factor β (TGF-β), platelet-derived growth factor (PDGF), insulin like growth factor-1 (IGF-1), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), connective tissue growth factor (CTGF) and so on[3]. They promote cell division and proliferation, increase collagen synthesis, stimulate angiogenesis, induce cell differentiation and remove necrotic tissue, to accelerate the wound repair and tissue regeneration. In addition, platelets release coagulation factors, serotonin histamine, endostatin and hydrolytic enzymes[4].

Autologous platelet-rich plasma

Autologous platelet-rich plasma (PRP) is plasma with a higher concentration of platelets than baseline. No definition exists as to that absolute number required, generally they are increased up to three to five times[5]. PRP is obtained by centrifugation of anti-coagulated blood. After centrifugation, the separated buffy coat layer, consisting of platelets and white blood cells, forms the PRP. PRP can release a variety of growth factors, so PRP can be used as in topical treatment as a biological agent in

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theory. Because of the chemotactic and mitogenic properties that promote and modulate cellular functions involved in tissue healing, regeneration and cell proliferation[6], PRP can be applied externally, added to implanted material or injected directly into a lesion as a matrix for regeneration. As an immediate effect, PRP will provide more rapid haemostasis and tissue adhesion by forming a fibrin clot, similar to fibrin glue. As the amount of released factors increases with the total number of platelets delivered to a site of injury, application of PRP increases the physiologic response to a trauma emulating and surpassing the "normal" deposition of growth factors and proteins in trauma[7].

Although platelets in PRP can release large amounts of the growth factor, they can only sustain in the early stage after preparation, approximately 8 h[8]. Long-term obvious impact was not observed. In the production process, platelets are stimulated by coagulant, platelet activator or shocked, and then platelets break down rapidly. The growth factors rise for a short period of time; therefore, the early impact of PRP is significant. At present, bovine thrombin and calcium chloride are used to inspire the PRP aggregation gel. However, bovine thrombin increased the risk of coagulopathy[9,10]. Clinical results reported with the use of PRP have been equivocal and possible, because most growth factors, such as TGF-β and PDGF, are released immediately from the PRP platelets, with significant reductions at days 3, 7, 14 and 21. This finding may explain the transient effect of PRP on wound healing[11,12].

PRF

PRF was first developed in France by Choukroun et al. in 2001. It can be considered as a second-generation platelet concentrate because the natural concentrate is produced without any anticoagulants or gelifying agents[13]. Therefore, this second-generation platelet concentrate eliminates the risk associated with the use of bovine thrombin. These technologies were tested in many different clinical fields, particularly oral and maxillofacial surgery, ear-nose-throat (ENT) surgery, ophthalmology, gynaecology, cardiovascular surgery, sports medicine, orthopaedic surgery and plastic surgery[14].

Classification of PRF

Choukroun's PRF (L-PRF) is the latest development of platelet concentrates protocols. In this protocol, 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 PRF (L-PRF) clot, without the need for any biochemical modification of the blood, so 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. However, some confusion is likely because different suppliers use similar nomenclature for their distinct products, such as Vivostat PRF and Fibrinet PRF Matrix (PRFM). Therefore, Ehrenfest et al. present classifications of the different platelet concentrates into four categories, depending on their leucocyte and fibrin content: pure platelet-rich plasma (P-PRP), such as cell separator PRP, Vivostat PRF or Anitua's PRGF; leucocyte- and platelet-rich plasma (L-PRP), such as Curasan, Regen, Plateltex, SmartPReP, PCCS, Magellan or GPS PRP; pure platelet-rich fibrin (P-PRF), such as Fibrinet PRFM; and leucocyte and PRF (L-PRF), such as L-PRF[15,16]. This classification should help us to elucidate successes and failures that have occurred so far, as well as providing an objective approach for the further development of these techniques.

Preparation of L-PRF

Unlike other platelet-rich products, the technique requires neither an anticoagulant nor bovine thrombin (or any other gelling agent). It is nothing more than centrifuged blood without any addition. The PRF protocol is very simple: a blood sample is taken without anticoagulant in 10-mL tubes, which are immediately centrifuged at 3000 rpm (approximately 400*g*) for 10 min (Process protocol, Nice, France)[13]. The resultant product consists of the following three layers: the topmost layer consisting of acellular PPP, PRF clot in the middle, RBCs at the bottom.

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 middle and upper part of the tube before the circulating thrombin transforms it into fibrin. A fibrin clot is then obtained in the middle of the tube, just between the red corpuscles at the bottom and acellular plasma at the top17. The PRF clot forms a strong fibrin matrix with a complex three-dimensional architecture, in which most of the platelets and leucocytes from the harvested blood are concentrated[18,19].

The success of this technique entirely depends on the speed of blood collection and transfer to the centrifuge. Indeed, without an anticoagulant, the blood samples start to coagulate almost immediately upon contact with the tube glass. 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[13].

Sometimes, a PRF membrane was needed in the applications of oral[20], maxillofacial[21,22], ENT[23] and plastic surgery[24]. The centrifuged PRF clot was picked up, and the red thrombus was eliminated along the border between this fraction and the PRF. Then, the PRF was usually compressed by

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dry gauzes, which became a strong membrane. Kobayashi et al. reports a novel PRF compression device. Compared to the PRF membrane compressed by dry gauze (G-PRF), the preservation of the plasma content, 3D-fibrin meshwork and platelets was more intact in the compressor-prepared PRF membrane (C-PRF). Among the growth factors tested, C-PRF contained PDGF isoforms at higher levels, and significantly stimulated cell proliferation and neovascularization. Therefore, PRF compressed by this compression device may be useful for grafting while minimizing the loss of bioactive factors[25].

Applications of PRF in plastic surgery

Recently, L-PRF and PRFM (P-PRF) were both applied in plastic surgery, and the applications can be divided into two aspects: facial plastic surgery and wounds healing (including surgical wounds, recalcitrant wounds, skin autografts, skin flap and so on).

Facial plastic surgery

The haemostatic, fibrogenic and angiogenic properties of PRF have been used in procedures such as rhytidectomy, rhinoplasty and facial implants, in which rapid healing, minimal oedema and reduction of ecchymosis are desired.

P-PRF: Sclafani et al. reported the applications of PRFM in facial plastic surgery, including periorbital treatments (crow's feet, tear troughs, suborbital hollows and glabellar furrows), midface and lower face treatments (malar augmentation, zygomatic arch enhancement, nasolabial folds, acne scars and boxcar acne scars) and adjuvant use of facial plastic surgery (facelift, rhinoplasty and facial implants)[26–28]. Finally, only a small percentage (10% or less) of patients do not generate a tissue response sufficient to produce a clinically acceptable result.

Because of the angiogenic abilities, PRFM has been co-injected during autologous fat transfer to enhance the viability and survival of the fat[26]. Evidence from the work of Sclafani and McCormick suggests that PRFM can also induce an anabolic state in mature fat as well as potentially promoting more rapid vascularization of the transferred fat[29]. PRFM is a significant new tool during minimally invasive as well as open surgical procedures.

However, once activated by calcium in the second tube during the preparation, PRFM begins to undergo fibrin polymerization. After 10 to 12 min, it is no longer possible to inject PRFM. Therefore, if using multiple tubes, activate only one at a time to avoid polymerization before use is necessary. PRFM must rely on the local tissues' ability to generate a cellular response, and may not be as effective in unfavourable wound conditions such as hypoxia or infection[26].

L-PRF: Choukroun's PRF has also been used in autologous adipose tissue transplantation. Liu et al. demonstrated that the adjuvant use of uncultured freshly isolated stromal vascular fraction (SVF) cells and autologous PRF prepared at the bedside can augment adipose tissue transplantation in a rabbit ear model[30].

Keyhan et al. compared the efficiency of first- and second-generation platelet-rich plasmas (PRP and PRF) combined with a fat graft during facial lipostructure surgery, and suggested that the combination of fat and PRF is more effective than the combination of fat and PRP in the context of facial lipostructure surgery. In the patients who were treated with the PRP/fat and PRF/fat techniques, a slight aesthetic asymmetry was noticeable, with more resorption on the PRP/fat side. The quality and stability of the graft through time are the most difficult factors to control because significant resorption (reaching 50% to 70%) can occur. The rapid neovascularization of grafted tissue is a major factor affecting cellular survival that also limits tissue resorption. The range of resorption was 10% to 33% in the cheekbone area[31]. There was no case of massive oedema, severe pain or prolonged bruising. Indeed, the deposit of a fibrin matrix in the grafted areas allows improved angiogenesis and thus superior vascular and lymphatic drainage. The risks of bruising and oedema also may be decreased. Undercorrection was the most frequent complication, perhaps due to an underestimation on the part of the surgeon at the time of the intervention or an excess adipocyte-mediated resorption.

Braccini et al. evaluated the effect of fibrin PRF clots in the adipocyte graft according to the technique of facial lipostructure described by Coleman[32], and suggested that the PRF could have a beneficial role on the cicatrization and the consolidation of an adipocyte graft by offering a matricial support to angiogenesis and stimulating the proliferation of pre-adipocytes. The hemi-face treated with PRF appeared more stable than the side without PRF. No important residual oedema or ecchymosis was seen on the third post-operative week[24].

Wound healing

In the clinic, a mount of literatures reported the effect of PRF in wound healing. Lundquist et al. suggested that the L-PRF could be beneficial for the healing of recalcitrant wounds by investigating the characteristics of L-PRF[33]. Jorgensen et al. also suggested the consistent results. A pilot trial on 15 patients, with 16 lower extremity chronic wounds of varying aetiologies, has been performed with a positive outcome[34]. Chignon-Sicard et al. investigated the efficacy of L-PRF in a randomized controlled clinical trial (RCT) of wound healing and demonstrated that a single L-PRF application on fresh postoperative hand wounds shows a median improvement of 5 days in comparison with the standard treatment[35].

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During PRF processing by centrifugation, platelets are activated and their massive degranulation implies a very significant cytokine release. By quantifying PDGF-BB, TGF-β1, and IGF-I within PPP (platelet-poor plasma) supernatant and PRF clot exudate serum. The analyses revealed that slow fibrin polymerization during PRF processing leads to the intrinsic incorporation of platelet cytokines and glycanic chains in the fibrin meshes[18]. Moreover, during PRF processing, leucocytes could also secrete cytokines in reaction to the haemostatic and inflammatory phenomena artificially induced in the centrifuged tube. By quantifying five significant cell mediators within PPP supernatant and PRF clot exudate serum: three pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α), one anti-inflammatory cytokine (IL-4) and a key growth promoter of angiogenesis (VEGF), the analyses revealed that PRF could be an immune regulation node with inflammation retrocontrol abilities[19]. This result would imply that PRF, unlike the other platelet concentrates, would be able to progressively release cytokines during fibrin matrix remodelling. This concept also could explain the reduction of postoperative infections when PRF is used as a surgical additive and the clinically observed healing properties of PRF.

Problems of PFR

This field of research unfortunately suffers from the lack of a proper accurate terminology and the associated misunderstandings, and the literature on the topic has been quite contradictory in the past, leading to many confusions in the scientific database. However, the future of this field is first dependent on the coherence and scientific clarity[14]. The classification presented by Dohan Ehrenfest et al. may be the key to solve this problem. This technological classification aimed to provide an overview of the available systems and to categorize them with respect to three main parameters: fibrin density, leucocyte content and degree of standardization of the procedure[15,16]. A terminology consensus can facilitate researchers to be aware of the complex nature of these living biomaterials, in order to avoid misunderstandings and erroneous conclusions.

The question of the leucocyte content within platelet concentrates for surgical use is in fact an old debate. There is however actually no proof that the leucocytes within these surgical preparations might have undesirable side effects. On the contrary, several studies showed that L-PRPs have antimicrobial effects[36], but no undesirable inflammatory reactions have been observed with L-PRPs up to now, even in immune-sensitive applications[37,38]. The influence of leucocytes injected with surgical platelet concentrates is actually a relevant way of research[39], and no author can claim that their influence is negative. All statements on this matter should be carefully and scientifically discussed and proven[40]. It is now important to demonstrate the influence of the leucocytes on the biology of each product and its potential benefits should now be carefully analysed because it could explain many controversial data from the literature.

PRFM (P-PRF) fundamentally differs from other PRP systems in that it promotes the physiologic functions of fibrin and avoids the potential drawbacks of included leucocytes. However, the simultaneous processing of large sample numbers with the Fibrinet method remains difficult and is expensive in daily practice. The so-called potential drawbacks of leucocytes are also lack of evidences and indeterminate. The development of PRFM may be limited in daily practice in future.

Prospection

PRF is an immune and platelet concentrate, collecting all the constituents of a blood sample favourable to healing and immunity on a single fibrin membrane. PRF allows the surgeon to directly deliver a concentrated and functional wound healing response to a target area, which can enhance the patient's natural wound healing ability. PRF can stimulate the production of viable blood vessels, fat cells and collagen deposits that seem to persist over time even without a wound.

L-PRF allows the production of a high quantity of L-PRF clots simultaneously using either a specific centrifuge that takes eight tubes or any modified laboratory centrifuge, making it possible to produce even more clots for larger surgeries. Another advantage of L-PRF is its low cost and the great ease of the procedure, which allows the production of many concentrates quickly and by natural means, that is, without the use of chemicals or unnatural conditions. Finally, expensive and complex procedures are often unusable in daily practice and many will disappear. Simple and free systems, such as L-PRF, were developed by clinicians for clinicians and are anticipated to be major methods in the next years. Therefore, L-PRF seems to be most suitable for widespread use in daily practice and is actually the main technique in some countries, including France, Italy, Israel and so on.

However, some literatures presented no significant negative effect of PRF in wound healing[41,42]. Further studies are necessary to validate the interest of the PRF in plastic surgery. The potential uses in plastic surgery of such a biomaterial, easy and fast to produce, without any high cost and with no risk, are very numerous and require from now on to be tested and validated methodically.

Critical appraisal of the validity of relevant articles

The Levels of Evidence of some relevant articles are Level II, whereas those of others are Level III in the EMB ranking system. Therefore, the validity of relevant articles is acceptable.

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Conclusion

PRF is the new generation platelet concentrate. PRF could be classified into two categories depending on its leucocyte content: P-PRF and L-PRF. PRF is obtained centrifugally by autologous peripheral blood, without adding any biological agents. PRF contains fibrin matrix polymer, leucocytes, cytokines and circulating stem cells. Because PRF is low in cost and is easily available, it has been applied in many different clinical fields, particularly oral and maxillofacial surgery, orthopaedic surgery and plastic surgery. L-PRF and P-PRF (PRFM) are both applied in plastic surgery and the applications can be divided into two aspects: facial plastic surgery and wound healing. However, the role of the leucocyte content within platelet concentrates for surgical use is still unclear. Therefore, further studies are necessary to unleash the confusion of PRF in plastic surgery.

Clinical applicability

In a clinical setting, PRF has been applied in facial plastic surgery and wound healing.

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