REVIEW ARTICLE

Biologic characteristics of platelet rich plasma and platelet rich fibrin: A review

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Abstract

The recent development of platelet concentrate for surgical use is an evolution of the fibrin glue technologies used since many years. Fibrin is a biologic glue that compact platelet clusters during coagulation process fibrin glues are biologic products that their local application has been used to decrease bleeding and accelerate tissue healing in the past three decades. Fibrin glue prepared based on a natural biologic mechanism (polymerization of fibrin during homeostasis) that reinforced by an artificial way. However, they were ever criticized because were blood derived products and had a high risk of viral infection the production of these products is based on the mixture of two plasma components including fibrinogen and thrombin. Platelet-rich plasma (PRP) is a fibrin matrix in which platelet cytokines, growth factors, and cells are trapped and may be released after a certain time. Choukroun *et al*. used platelet rich fibrin (PRF) protocol in oral and maxillofacial surgery to improve bone healing. Autologous PRF is considered to be a healing biomaterial, and presently, studies have shown its application in various disciplines of dentistry. PRF is the second generation of platelet concentrates which allows fibrin membranes to get enriched with platelets and growth factors, starting from an anticoagulant free blood harvest. PRF is similar to a fibrin network that allows cell migration and proliferation, and consequently, a more efficient cicatrization. Many growth factors, such as platelet-derived growth factor and transforming growth factor, are released from PRF. One of the major differences between PRF and PRP is the different polymerization that is responsible for the different biologic properties. PRF released autologous growth factors gradually and expressed stronger and more durable effect on proliferation and differentiation, which means that PRF could stimulate the surrounding environment to a more rapid wound healing. This review aims to evaluate the effect of biologic characteristics of fibrin glues, PRP, and PRF.

Keywords: Fibrin, platelet rich fibrin, platelet rich plasma

Introduction

One of the researchers' great challenges is to obtain bioactive surgical additives to modulate inflammation and increase healing. After each surgical intervention, surgeons confront the complex phenomenon of tissue remodeling and the effects of it on healing. Although the application of fibrin glues was explained more than 30 years ago,[1,2] because of complex preparation protocol and also the risk of cross infection and its usage is still controversial. Development of platelet concentrating technique and enhanced efficacy of protocols lead to produce new fibrin glue were known as platelet-rich plasma (PRP) but due to legal limitation for the usage of blood products; a new generation of concentrating platelets that was nor fibrin glue neither concentrating platelet introduced in France. This new product named platelet rich fibrin (PRF) was like an autologous cycatrical matrix.

Fibrin

The fibrin is a biologic glue that compact platelet clusters during the coagulation process. Fibrinogen is the final production of coagulation reaction and it is a soluble protein that by thrombin is converted to fibrin. Fibrin polymerized gel is the first matrix formed at the wound site.[3,4]

Fibrin and surgical additives

Fibrin glue prepared based on a natural biologic mechanism (polymerization of fibrin during homeostasis) that reinforced

by an artificial way.[5] However, they were ever criticized because were blood-derived products. Pharmacologic products had a high risk of viral infection, but today simple ways are introduced for production of fibrin autologous glues based on the development of platelet concentrating technique[6] that these products act similarly to the final stage of coagulation cascade that fibrinogen converts to fibrin.

Clinical use

Despite significant differences between protocols, most of the studies showed the high efficacy of fibrin glues for controlling of slow and widespread bleeding of fibrin parenchyma but these products cannot be effective for sever vascular bleeding.[2] These glues successfully used to stop widespread microvascular bleeding and are famous of their ability to seal wound borders.[7] Surgeons use the mechanical properties of these products in addition to their biologic benefits.[8-10] Sealing with fibrin glues caused reduction of hematoma before the surgery.[11] The usage of fibrin products completely explained for plastic and maxillofacial surgery.[7-10] However, many surgeons used this glue in different surgeries on animal models and the results were contradictory specially for orthopedic and neurosurgery.[12] Sealing of dura mater or nerves for reconstruction in trauma or tumor surgery was not explained in literature. It showed that these products are not more than autologous fibrin glues that their major role is only connection of tissues.[12,13]

Concentrated PRP

Due to the risk of hepatitis infection, production of fibrin products has been prevented in USA from 1978[14] Hence, the combination of concentrated platelet products with the idea of cell therapy with growth factors proposed.[14] Concentrated platelets were used for prevention and treatment of bleeding caused by thrombopenic condition like maxillary aplasia and acute leukemia and their usage was limited.[6,15] The production protocol of PRR are based on two centrifugation for increased platelet aggregation. According to this protocol, the blood sample collected before surgery immediately centrifuged to concentrated platelets.[16] Then, thrombin and calcium chloride added to activate platelets and produced gel.[17-20]

Platelet concentration of plasma is 3-5 times more than human plasma.[21] Platelets have a major role on homeostasis and are a natural source for growth factors. Activation of platelets with different factors like thrombin, calcium chloride or collagen causes the release of growth factors. Growth factors have a key role on wound healing, regeneration, chemotaxis, proliferation, differentiation, and angiogenesis.[22] Platelets also release factors, such as fibronectin, vitronectin, and sphynosins-1-phosphate, that are effective for healing process.[23] In addition to release of different factors PRR forms a fibrin network that acts as a regeneration matrix.[24,25] PRR used for soft and hard tissue augmentation, because increases vascularization of grafts, improves soft tissue healing, decreases the mobility, and increases bone regeneration.[26] Improbable cross infection, immunologic reaction is another advantage of PRR.[27] PRR makes the handling of grafted material and packing of them more easier and increase the maintenance of space and bone regeneration potential.[28,29] Since PRR contains different growth factors, it stimulates angiogenesis and fibroblast differentiation. Hence, it recommended for improvement of soft tissue healing.[30] Studies showed that PRR increases the concentration of grafts and decreases its micron scale movement that provides and appropriate environment for a successful graft.[31] PRR increases wound maturation and epithelialization and decreases scar formation.[32] Epidermal growth factor and platelet-derived growth factor are the major growth factors responsible for fibroblast migration and collagen synthesis. Increased concentration of these growth factors are the probable causes of increased wound healing that it estimated 2-3 times more than normal situation.[32] In hard tissues growth factors affect osteoblast. The addition of PRR to stromal cells in animal model approved its angiogenic and osteogenic properties.[33] Studies showed the successful use of PRP for bone regeneration in periodontal defects, extracted sockets, implant surgery, and sinus augmentation.[34] One of the major challenges of bone augmentation is the prolonged healing period, so one of the important indications of PRP is to reduced healing period. Shorter time needed for grafts healing in sinus augmentation showed in studies.[32,33] Increased regeneration of bone in periodontal defects at the distal aspect of 2nd molar after surgical removal of 3rd molar had been reported in studies.[34,35] But unfortunately, these results were not complete because the biopsy cannot be taken from the site. In human studies, use of PRR increased bone healing and regeneration.[16,26] Short period of improvements of bone regeneration (for 2 weeks) was seen in sinus augmentation.[36] Only when target cells like osteoblast and osteocyte are present at the site, bone regeneration can occur.[37] Because studies used the combination of non-organic grafts with PRR did not show any benefit in different follow-up periods.[36] In animal studies when spongy bone of iliac crest used as the graft material for sinus lift with PRR the clinical results in case and control group was similar.[28,38] One of the results put forward the less than expected effects of PRR in studies, may be that concentration of growth factors in PRR is much less than expected effects of PRR in studies, may be that concentration of growth factors in PRR is much less than the value that has clinical effects. It seems that the cytokines potential that release during the platelet activation and fibrin network formation is extremely limited.[39,40] It expected that fibrin network acts as a supportive matrix for cytokines, but these soluble molecules release so fast that they cannot place into this structure.

PRF

PRF was used for the first time by Choukroun *et al.*[41] in oral and maxillofacial surgery. This technique did not require to anticoagulants, thrombin and any other jellying factor and it was not anything except a centrifuged blood product without any other additives that was not included the laws about the

prohibition of blood born products. Only a PC-Q2 centrifuge and a kit are needed for PRF production. PRF preparation protocol is very easy. The blood samples collected without any anticoagulants and immediately centrifuged at 3000 rpm for 10 min. Not the usage of anticoagulants causes platelet and coagulation cascade as a result of its contact to the wall surface within minutes and platelet trapped in the fibrin network. Fibrin clot achieved at the middle part tube between red blood cells in the bottom and acellular plasma in upper. The success of this technique is dependent on the fast collection of blood sample and its transfer to the centrifuge. Without use of anticoagulants, the sample should be centrifuged within minutes otherwise the fibrinogen cannot be concentrated in the middle and upper part of tube. It is necessary to concentrate fibrinogen before thrombin convert it to fibrin. Hence, the fast preparation of this protocol is the key tip to achieve a useful PRF clot. The most important property of this technique is not usage of anticoagulants that leads to extensive platelet activation and release of large amounts of cytokines that these soluble molecules trapped into fibrin network.[42] One of the major differences between PRF and PRR is the different polymerization that is responsible for different biologic properties. The addition of thrombin and calcium chloride in PRP causes rapid polymerization, but PRF polymerization is slow and natural and thrombin activity is physiologic. The addition of bone thrombin in PRP leads to formation of compacted tetra molecules with bilateral connections and thickened polymerizes fibrin that is not appropriate for cytokine placement and cell migration. But its high strength is suitable for sealing the tissues. Tri molecules mono lateral connection formed in PRF due to physiologic concentration of thrombin that forms a flexible network that is appropriate for cytokine storage and cell migration and because of its flexibility they are used as membranes.

Conclusion

Platelets contain important growth factors that increase cell proliferation, collagen production, chemotaxis, angiogenesis, and cell differentiation. PRP and PRF are concentrated platelets suspension in a small amount of plasma. Moreover, PRP and PRF contain three adhesive molecules (fibrin, fibronectin, and vitronectin) that reinforced osteoconduction. The major difference between these two products is their polymerization that leads to their different biologic characteristics. Polymerization of PRP is induced by addition of anticoagulants but PRF polymerization is a natural and slow process. Hence, PRF has more suitable fibrin network for storage of cytokines and growth factors and also cell migration.

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