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Fibrin Glue as a Cell-Delivery Vehicle in Wound Healing

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Abstract

The human body built with hard and soft tissue which has a fairly remarkable inherent capacity for regeneration; however, this regenerative capacity has its limitations, and defects larger than a critical size lack the ability to spontaneously heal. As such, the development and clinical translation of effective tissue regeneration modalities are paramount. One regenerative medicine approach that is beginning to gain momentum in the clinical setting is the use of platelet-rich plasma (PRP). PRP therapy is essentially a method for concentrating platelets and their intrinsic growth factors to stimulate and accelerate a healing response. While PRP has shown some efficacy in both in vitro and in vivo scenarios, to date its use and delivery have not been optimized for tissue regeneration. Issues remain with the effective delivery of the platelet-derived growth factors to a localized site of injury, the activation and temporal release of the growth factors, and the rate of growth factor clearance. This review will briefly describe the physiological principles behind PRP use and then discuss how engineering its method of delivery may ultimately impact its ability to successfully translate to widespread clinical use.

Keywords: Regenerative medicine; Blood plasma; Cell-extracellular

Introduction

PRP is a concentration of platelets in blood plasma. In a healthy human, average circulating platelet counts are approximately 200,000 platelets/μL. Clinically, PRP is typically administered at a several 7 fold increase over that baseline concentration. The interest in concentrated platelets is derived from their early role in the normal healing response. Platelets contain more than 300 biologically active molecules which are released upon activation and subsequently influence the tissue regeneration process. Activated platelet-derived factors serve as messengers and regulators that influence a variety of cell-cell and Cell-Extracellular Matrix (ECM) interactions [1-5]. In addition, it has been shown that a linear relationship exists between platelet concentrations and the concentration of available cytokines. This is attractive to tissue engineering and regenerative medicine since increasing the number of platelets available in a defect/injury site will increase the amount of bioactive cytokines capable of stimulating and accelerating the repair process [6-8].

Platelet alpha and dense granules release an array of bioactive molecules upon activation. Activated PRP contains Platelet-Derived Growth Factor (PDGF), transforming growth factor-β (TGF-β), Vascular Endothelial Growth Factor (VEGF), Epidermal Growth Factor (EGF), Fibroblast Growth Factor (FGF), and others. PRP also contains a number of macrophage and monocyte mediators and a variety of Interleukins (IL) capable of mediating inflammation. Furthermore, the plasma component of PRP contains the proteins fibrinogen, albumin, several immunoglobulins, and more. Several of these bioactive molecules play a significant role in tissue remodeling [9,10].

The clinical use of PRP has expanded into treatment of multiple tissues, albeit with varying degrees of effectiveness. PRP therapy (in various delivery methods) has been implemented to stimulate tissue regeneration in bone, cartilage, skin, ligament, tendon, muscle, and more. This therapy typically involves an autologous blood draw and centrifugation to separate and obtain the platelet concentrate. PRP is then activated (commonly by $CaCl_2$ and/or thrombin) and applied to the defect/injury site. However, it has been shown that thrombin as a clotting agent to form a platelet gel can result in rapid activation of platelets and ultimately a mass release of growth factors (70% released within 10 minutes and nearly 100% released within 1 hour). These growth factors, which undergo a burst release, are cleared before they can have any stimulatory effects on cells. When platelet gels are formed using $CaCl_2$, growth factor release can be slowed. $CaCl_2$ activates and clots PRP by forming autogenous thrombin from prothrombin leading to the eventual formation of a loose fibrin matrix that will release growth factors over 7 days. As for example in bone regeneration this is a lengthy process (adequate strength typically restored within 3-6 months), there is an obvious need for effective delivery vehicles capable of the sustained release of PRP-derived factors over an extended period of time to maximize their regenerative potential. This review details the regenerative advantages of PRP and examines various techniques and scaffolding options for the sustained delivery of PRP-derived growth factors to diseased or damaged tissue [11-15].

Fibrin Glue as a Delivery System for Growth Factors

Fibroblasts and endothelial cells will readily migrate into fibrin clot. This process of migration and subsequent proliferation is controlled by a variety of growth factors. Exogenous growth factors have been used experimentally to modify wound healing. Fibrin glue provides a useful carrier, which both delivers the growth factors to the wound and releases them at a steady rate. It also acts as a scaffold for subsequent tissue regeneration.

Overview of Fibrin Sealants

Fibrin sealants (also known as tissue adhesives or glues) are designed to mimic the final steps of the blood coagulation cascade, forming a stable, physiological fibrin clot that assists homeostasis and wound healing. Fibrin sealants are derived mainly from blood plasma and contain necessarily fibrinogen and thrombin. Further ingredients

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are anti-fibrinolytic agent (such as aprotinin), and calcium chloride. Some fibrin sealants also contain factor XIII. Fibrinogen is broken down to fibrin monomer by the action of thrombin. The fibrin monomer then polymerizes in the presence of factor XIII and calcium to form a fibrin polymer, which is precipitated as fibrin fibrils in the tissue. The fibrin polymer is broken down to fibrin degradation products by plasmin (which is inhibited by aprotinin) and bacterial proteolytic enzymes (Figure 1) [16,17].

Fibrin sealants are used mainly for topical homeostasis, suture support and tissue adhesion. They are used

- to assist homeostasis in a bleeding field
- to reduce blood flow from solid organs
- to help seal suture holes
- to help seal anastomosis or leaks from hollow organs
- to assist or replace sutures in surgical procedures, particularly where suturing is difficult or impossible.

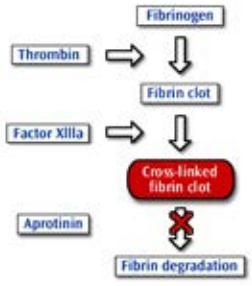
New and novel uses for fibrin sealant are still being developed; some of the more recent uses include tissue engineering and drug delivery

For many years specialists have prepared autologous fibrin sealant based on thrombin and fibrinogen.

The first experiments in the use of fibrinogen as a tissue adhesive were carried out in 1940. The concept of fibrin glue became realistic in the 1970's, with the advent of techniques for isolation and concentration of coagulation factors. In 1972, the success of fibrin glue in repairing a peripheral nerve was described. Since then, there have been many reports of successes and the use of fibrin glue has been extended into several areas of medicine (Figures 2 and 3).

Many surgeons have indicated fibrin glue as the ideal sealant material and because of its human origin it is not toxic towards tissue. Fibrin glue promotes firm adhesion in seconds or minutes; it is reabsorbed within a few days after application

Autologous fibrin glue may be produced from a sample of blood with citrate drawn from the patient. Fibrinogen is obtained from platelets poor plasma via centrifugation of blood and autologous thrombin is prepared by taking a blood sample without citrate and add Cacl2 (Figures 4 and 5).



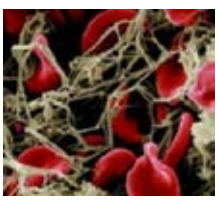


Figure 1: Factors influencing fibrin deposition and breakdown.

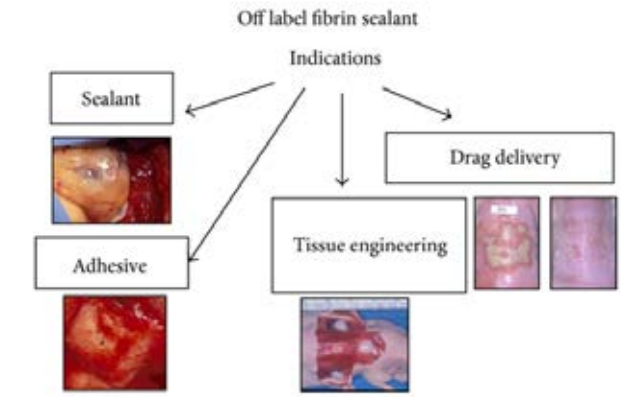
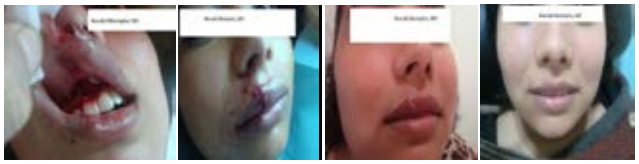
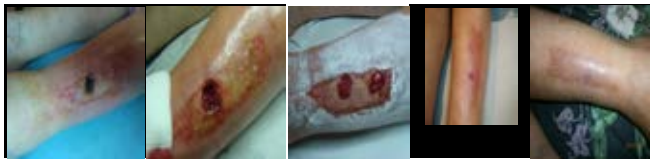


Figure 2: The off label indications for fibrin sealant [8], adapted and reprinted with kind permission from Springer Science + Business Media in ref. [8].



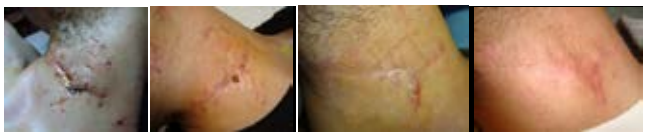
At presentation. Fibrin glue + partial sutures. 2 weeks follow up. 4 weeks follow up.

Figure 3: Avulsive wound over upper lip of a 19 year old female from motor-vehicle accident.



Day1. Post-debridement. Fibrin glue deposition. 4 weeks follow-up. 6 weeks follow-up.

Figure 4: Dry gangrene lesion of 3cm in width and 2 cm in depth over left leg in an 85 year old female post-traumatic fall in the subway.



Day 1. 2 weeks follow-up. 3 months follw-up. 6 months follw-up.

Figure 5: Open-wound lesion in a 27 year old male Post-traumatic knife stabbing in the neck.

Procedures of making autologous thrombin are by following

1. Withdraw 4-5 ml of autologous blood with untreated tube.
2. Stand the tube and place calmly for 30 min.
3. Then centrifuge the tube under condition on 3600 rpm for 12 min.
4. Collect the supernatant as autologous thrombin.
5. Mix autologous thrombin with 10% $CaCl_2$.

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