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AUTOLOGOUS PLATELET CONCENTRATE ENRICHED WITH GROWTH FACTORS (APC+): A MORE BIOACTIVE HEMOSTATIC AGENT THAN FIBRIN GLUE

The response of living tissue to injury forms the foundation of all surgical practice. The wound-healing process is routinely divided into three phases (inflammatory, proliferative, and remodeling) and involves a complex intercommunication between a wide variety of cells. Following initial tissue injury, hemostasis is the first step of the inflammatory phase. Although several techniques help achieve hemostasis after initial injury, few initiate and actually accelerate tissue regeneration. One evolving technique is the use of autologous platelet concentrates enriched with growth factors (APC+™).

APC+ and fibrin glue have both been shown to be effective hemostatic agents (*1*). However, unlike fibrin glue, the concentrated platelet alpha granules found in APC+ contain huge reservoirs of bioactive proteins, including growth factors, that are vital to initiate and accelerate tissue repair and regeneration. The APC+ prepared using the **Harvest®** **SmartPReP™** system, (Harvest: Technologies Corp, Plymouth, MA), when combined with thrombin, produces a bioactive platelet gel or "**SmartClot™**". To understand the difference between a **SmartClot** and a "fibrin glue" clot, it is important to understand the characteristics of each clot.

A fibrin glue clot is comprised of cross-linked fibrin strands that form a matrix structure. The fibrin matrix provides a scaffold into which undifferentiated cells from the surrounding tissue, such as fibroblasts, can migrate (*2*, *3*). However, the quantity and quality of the fibrin strands in some commercial preparations may produce such a dense architecture that angiogenesis and overall healing is inhibited (*4*). In addition, the fibrin glue matrix is considered bioactively passive in that it does not possess a mechanism to actively recruit undifferentiated cells into the scaffold. Although these characteristics do not affect the fibrin clot's hemostatic properties, they can result in delayed and defective tissue repair.

Conversely, the **SmartClot** is composed not only of cross-linked fibrin strands but also of a high concentration of platelets that bind to each other and the fibrin strands. The platelets in the matrix contribute to overall clot strength. It has been shown that 55% of the clot strength is due to the platelets and 45% is due to the fibrin strands (*5*). Because the fibrin strands in **SmartClot** are not increased above normal levels, the matrix structure that is formed has the same open architecture of a typical blood clot and is conducive to ingrowth of new capillaries.

The **SmartClot** is also considered a bioactive matrix because of its concentration of platelets. Elevated platelet levels play a very important role in tissue healing and the platelets' role in tissue regeneration is well documented. The platelets become activated as the matrix forms and they release a multiplicity of growth factors into the matrix (*6*, *7*). The action of these growth factors is what makes the matrix bioactive. The growth factors released in the **SmartClot** are active in two ways that affect tissue regeneration: First, the growth factors actively attract undifferentiated cells into the matrix where the undifferentiated cells attach themselves to the matrix's fibrin strands. Second, the growth factors then bind to the cell membrane of fibroblasts or other undifferentiated cells and, through the process of signal transduction, they trigger cell division (*8-10*).

In addition to growth factors, the **SmartClot** contains additional proteins considered critical to initiating tissue regeneration. The plasma contains several adhesion molecules that play a role in facilitating the binding of undifferentiated cells within the clot matrix. The platelets

Protein	Biological Activity	Fibrin Glue Clots	Smart Clot
Fibrinogen	Promote hemostasis, provides scaffolding for undifferentiated cell migration	Yes	Yes
Adhesion Molecules (Fibrinectin, SCF, vitronectin)	Facilitate intercellular binding and communication	No	Yes
Platelets	Promote hemostasis, initiate wound healing cascade	No	Yes
Platelet Protein (IL-1β)	Signals lining cells of damaged vessels to display receptors for macrophages	No	Yes
Platelet Derived Growth Factors (PDGF)	Initiate connective tissue healing, increases mitogenesis, angiogenesis, and macrophage activation	No	Yes
Transforming Growth Factor Beta (TGF-β)	Increases the chemotaxis and mitogenesis of osteoblast precursors; stimulate osteoblast deposition of the collagen matrix of wound healing and bone regeneration	No	Yes
Epidermal Growth Factors (EGF)	Induce epithelial development and promote angiogenesis	No	Yes
Vascular Endothelial Growth Factors (VEGF)	Contain potent angiogenic, mitogenic, and vascular permeability enhancing activities specific for endothelial cells	No	Yes

also produce signaling proteins that attract white blood cells. The biological functions of several key proteins are listed in the table above.

There are many possible methods for making autologous platelet concentrate. In order to achieve a bioactive matrix with an APC+ clot, it is important that the process used in obtaining the platelet concentrate yield viable platelets (*11*). The data presented at the Society for Biomaterials meeting by Sherwin Kevy, M.D., Director, Center for Blood Research Laboratories (Boston, MA), showed platelets concentrated using the **SmartPReP** system had characteristics similar to the requirements of the American Association of Blood Banks for transfusable platelets. Dr. Kevy states, ***"To my knowledge, only the Harvest SmartPReP system has published data documenting the characteristics of the platelets present in its platelet concentrate."***

Dr. Kevy has also shown in an in-vitro model that the growth factors released by the concentrated platelets from the **SmartPReP** system remain active for seven days (*12*). Any methodology for producing a platelet concentrate that cannot offer similar proof of platelet viability is not likely to produce the critical bioactive matrix with its APC+.

Patient safety issues will always be a concern when using blood components. Although the pooled, human-derived fibrinogen and thrombin found in commercial fibrin glues are processed to remove and inactivate viruses, the potential to transmit infectious agents cannot be totally eliminated. Unlike fibrin glues, the platelets and fibrinogen that comprise the **SmartClot** are autologous. In addition, the platelets and fibrinogen are harvested, as well as applied, point-of-care, from the patient to the patient, thereby eliminating the risk of transfusion-related diseases.

Even the use of bovine-derived agents such as aprotinin (clot stabalizer for fibrin glues) or thrombin (activator for APC+) can be of concern to some physicians because the risk of a patient developing sensitivity to bovine materials cannot be totally eliminated. However, a literature review resulted in only one published paper discussing the occurrence of elevated antibody levels to human coagulation proteins when used as a hemostatic agent (thrombin) in surgery (*13*). The current commercially available thrombin (Jones Pharma, Inc. USA) is chromatographically purified and, to date, no reports have appeared in the medical literature indicating that the JMI product has resulted in antibody to human coagulation proteins.

In summary, the use of surgical glues and autologous platelet concentrates are revolutionizing many surgical fields. However, only APC+ provides both hemostatic properties and valuable tissue regeneration proteins to accelerate the healing process.

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