Autologous Platelet Gel and its Clinical application

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Abstracts: Platelets are attracted to a wound or injury site stimulating the clotting and healing cascades. Degranulated platelets release numerous substances including proteins known as growth factors. Growth factors signal undifferentiated stem cells to the site, promote cell mitosis, and stimulate osteogenesis and angiogenesis. Cytokines, which attract neutrophils, are also released from platelet granules. Concentrating platelets 4x to 5x the baseline level accelerates the healing process. When platelet rich plasma is mixed with an activator, a platelet gel will form. Clinical applications of platelet gel are numerous. Some benefits include a marked decrease in post-surgical swelling and bruising, reduction in surgical site pain, elimination of drains, and acceleration of bone growth and soft tissue healing. Scientific publications support that autologous biomaterial accelerates the healing process. [Jain P et al NJIRM 2012; 3(3) : 165-169]

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History: Autologous platelet gel (APG) was developed in the early 1990's as a byproduct of multicomponent pheresis when platelet concentrate is combined with thrombin and calcium, a viscous coagulum (gel) is rapidly formed. Initial successes lead to expanded applications where large blood losses were not typically encountered. Because it is autologous, PRP avoids the risk of transmissible diseases such as HIV, Hepatitis B, C, or D, and other blood borne pathogens. Because it is used topically in and on top of a wound in a clotted fashion, it never re-enters the individual's circulation. It is therefore safe when clot accelerators such as bovine thrombin are used or when PRP is added to other materials such as bovine collagen, gelfoam, PLA-PGLA constructs, etc.

The Basic Biology of Platelet Growth Factors: Since 1990, medical science has recognized several components in blood which are part of the natural healing process and if added to wounded tissues or surgical sites as a concentrate have the potential to accelerate healing. These specific components in blood include platelet derived growth factor (PDGF) and transforming growth factor beta (TGFß), both of which are contained within the alpha granules of platelets, and fibronectin and vitronetin, which are cell adhesion molecules found in plasma, and fibrin itself. It is widely accepted that growth factors play a central role in the healing process and tissue regeneration.[1] This conclusion has lead to significant research efforts examining varying growth factors and their role in repair of tissues [2,3] [4,5,6,7,8,9] However, there are conflicting reports in the literature regarding potential benefits. Although some authors have reported improved bone formation and tissue healing with PRP, others have had less success.[6, 7, 8] These varying results are likely attributed to the need for additional standardized PRP protocols, preparations, and techniques. A laboratory analysis of human PRP samples demonstrated increased concentrations of platelet-derived growth factor (PDGF), transforming growth factor beta (TGF-b), vascular endothelial growth factor (VEGF), and epithelial growth factor (EGF).[4, 5, 6,7,8,9] Alpha granules are storage units within platelets, which contain pre-packaged growth factors in an inactive form. The main growth factors contained in these granules are TGF-b, VEGF, PDGF, and EGF. The granules also contain vitronectin, a cell adhesion molecule which helps with osseointegration and osseoconduction. TGF-b is active during inflammation, and influences the regulation of cellular migration and proliferation; stimulate cell replication, and fibronectin binding interactions.[9, 10] VEGF is produced at its highest levels only after the inflammatory phase, and is a potent stimulator of angiogenesis. Anitua et al. showed that in vitro VEGF and Hepatocyte Growth Factor (HGF) considerably increased following exposure to the pool of released growth factors;

suggesting they accelerate tendon cell proliferation and stimulate type I collagen synthesis.[11]

Platelet Derived Growth Factor (PDGF): Platelet Derived Growth Factor is the evolutionary sentinel growth factor that initiates nearly all wound healing. It exists in three dimeric forms: **PDGFaa, PDGFbb, and PDGFab**. Platelet derived growth factors' main functions are to stimulate cell replication of healing capable **stem cells** and what are also called pre-mitotic partially differentiated **osteoprogenitor cells** which are also part of the connective tissue-bone healing cellular composite. It also stimulates cell replication of endothelial cells. This will cause budding of new capillaries into the wound, a fundamental part of all wound healing. In addition, PDGF seems to promote the migration of perivascular healing capable cells into a wound and to modulate the effects of other growth factors.[5]

Transforming Growth Factor-beta (TGFß): The so-called "super family" of TGFßs numbers about forty seven, and includes all of the well-published bone specific morphogen growth factors of the 13 known Bone Morphogenic Proteins (BMPs). The type of TGFß found in platelets is **TGFß1** and **TGFß2**, which are the more generic connective tissue growth factors involved with matrix formation (i.e. cartilage and bone matrix as well as vascular basal lamina matrix.) Cells which are activated by TGFß1 or TGFß2 include fibroblasts, endothelial cells, osteoprogenitor cells, chondroprogenitor cells, and mesenchymal stem cells. If a fibroblast is "activated" it will undergo cell division and produce collagen. An endothelial cell will be stimulated to produce new capillaries. An osteoprogenitor cell will further differentiate and produce bone matrix. A chondroprogenitor cells will further differentiate and produce the matrix for cartilage. A mesenchymal stem cell will be stimulated to mitose so as to provide the large population of wound healing cells needed for completion of healing.[13, 14]

Clinical Applications of Autologous Platelet Concentrate: The clinical applications for APC are numerous. Currently, large randomized studies are taking place and being reported. A review of some clinical applications follows.

Oral and Maxillofacial Surgery: Platelet gel is applied to mandibular bone graft to accelerate bone growth for dental implants. Clinical observations have shown radiographic density and maturity of bone approximately twice that of grafts without PRP. “PRP accelerates the rate of bone formation and allows earlier return of function and earlier implant placement.”2 Mixing allograft or synthetic graft material with PG will make a more bioactive bone graft material. Other areas of use include surgical repair of alveolar clefts, oral-nasal fistulas, and procedures involving endosseous dental implants.[11, 14] PRP has been used for PG in patients undergoing elective impacted mandibular third molar extractions. The overall rate of alveolar osteitis in PRP treated site was 3.4% vs. 12.8% in the untreated site.[16]

Neurosurgery: Platelet gel can be used as a biologic sealant in an effort to create a watertight dural closure. This is to prevent a CSF leak or to repair a documented leak in surgeries such as pituitary tumor removal, skull base tumor resection, acoustic neuroma excision, and intradural procedures involving tumor or release of tethered cords. In a Stanford University study, PG was used as an alternative to fibrin glue in dural wound repair with 39 of 40 patients having successful repair.[17]

Facial Plastic & Reconstructive Surgery: Platelet poor plasma and PRP are widely used in these surgeries. Both products are activated with thrombin/calcium activator solution. Once activated, the PPP forms fibrin glue. It can be sprayed on exposed surfaces for hemostasis as well as in the surgical bed to decrease bleeding. Platelet poor plasma is applied to the undersurface of facial flaps serving as an adhesive. Gauze is rolled along the flap to spread the gel and remove any excess fluid.[18] Some applications of PG include facelifts, endoscopic browlifts, blepharoplasty (eyelids), rhinoplasty, incision lines, skin grafts, bony reconstruction, and bone graft donor sites. Decrease in postoperative swelling, hematoma formation, seroma formation, and healing time have been reported.[19] Spraying PG as a biologic dressing after CO2 laser resurfacing significantly reduces bleeding, bruising, decreases post-operation pain, and speeds healing and recovery in

patients.[20] Early wound healing with quick epithelialisation was noted in the PRP wounds.

Otolaryngology-Head & Neck Surgery: During radical neck dissections and pectoralis mayor myocutaneous flaps, PG is used as a hemostatic agent and lymphatic sealant. Less post operative drainage allows for early removal of the drains. Platelet gel has been used in endoscopic paranasal sinus surgery as a packing material with excellent results.[21]

Orthopedic Surgery: Total hips, total knees, and iliac crest harvest sites all benefit from the use of PG. When used in total knee arthroplasty (TKA), benefits include earlier functional range of motion, decreased IV and oral narcotic requirements, and lower drop in hemoglobin.[22] Enhancement of fusion has been observed in total knees and lumbar fusions.[23,24]

Chronic Wounds: An impressive office-based study of chronic wounds was performed. The wounds included diabetic ulcers, debubitis ulcers, venous stasis ulcers, and complicated surgical wound dehiscence. Included in the study were patients with a wound that failed to have any reduction in size after 4 weeks of standard treatment. Sixteen patients with 17 wounds were enrolled in the study. The number of aulologous platelet concentrates applications varied. There was successful wound closure in 16 of 17 wounds. There was a 94% success rate with criteria for success being complete epithelization.[25] In a randomized control-designed study of 20 decubutis ulcers, PG was found to promote wound healing in the treatment group compared to those wounds that did receive conventional therapy.[26]

Major Vascular Surgery and General Surgery: Vascular access grafts, abdominal aortic aneurysm, carotid endarterectomy are vascular surgeries that benefit from the use of PG. Laproscopic cholecystectomy, splenectomy, gastrectomy, pancreatic, liver resection, hernia repair, mastectomy, limb amputation, and numerous other general surgeries have also shown benefit from PG application.

Cardio-Thoracic: Platelet gel is widely used in the areas of coronary artery bypass grafts surgeries for leg and arm wounds. It is also used in valve repair/replacement, sterna repair, aneurysm repair, and cardiothoracic surgeries.

Urology: Platelet gel may be used during radical retropubic prostatectomy and retroperitoneal lymph node dissections. Decreased drain outputs and postoperative fluid requirements have been observed. Also noted was the trend toward early discharge from ICU, less post operative blood transfusions, and early drain removals.[15]

Plantar fasciitis, sometimes called “heel pain,” is the most commonly treated condition by podiatrist and foot specialist. In a small study, only APC (not gel) was injected into the feet using high-resolution diagnostic ultrasound for guidance. Both pre- and post ultrasound measurements of medial, central, and lateral bands were obtained. Decrease in thickness of the symptomatic medial band and resolution of pain was noted for all patients.[27]

Conclusion: Platelet-rich plasma represents an emerging biotechnology in current tissue engineering and cellular therapy. Acceleration of bone growth and soft tissue healing has been well documented. Autologous blood yields a product that is safe and free from transmissible diseases. With proper preparation, large numbers of platelets in the PRP are activated producing high concentrations of GF which stimulate soft tissue growth, osteogenesis, and angiogenesis.

Many manufactures have presented equipment to process anticoagulated blood to PRP. When researching these clinical devices used to prepare PRP, one must consider a clinical system that result in platelets comparable to those which are produced for transfusion therapy. If minimal platelet activation and functional viability is maintained, maximum GF will be released within 1 hour of activation and continue to be released for 1 week. Benefits of PG include decreased pain and pain medication, decreased bleeding, bruising and swelling, reduction or elimination of drains, increased bone graft regeneration, and soft tissue healing. Clinical applications of PPR include oral and maxillofacial, neurosurgery, facial plastic, reconstructive surgery, otolaryngology, orthopedic, chronic wounds, major vascular, general surgery,

cardiothoracic, ophthalmology, urology, and veterinary hospitals. Burns, snake bites, and spider bites that have been properly debrided show excellent results. Reimbursement issues are being addressed. Greater understanding of the effects of PRP will come from the large, randomized studies that are underway and being reported.

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