The Current Use of Platelet Rich (Leukocyte) Plasma in Surgical and Wound Applications

Paul W. Buza D.O., A.C.N., A.M.E.

Summary Review

The utilization of platelet rich plasma (PRP) in a variety of surgical and wound care settings is now quite extensive throughout the United States and European communities. Further discussed is a general review of the history and scientific research that has led to its current use. Included are the reverences of the scientific papers that support the use of PRP. These papers fall into different subcategories which include: growth factors within the wound healing cascade, bio-tissue engineering for autologous and allogenic tissue grafts, surgical application of PRP in a wide variety of procedures, growth factor therapy for osseous bone integration and soft tissue regeneration. Also attached are the protocols for utilization and review of quality control and safety profiles.

Over the past 25 years different emerging technologies have developed leading to the current use of PRP. In the late 1970's, the importance of growth factors within the wound-healing cascade were identified. These began with platelet-derived growth factor (PDGF) and the subsequent identification of many other growth factors now known to be important within different stages of the wound-healing cascade. These stages of wound healing include the inflammatory, proliferative and remodeling phases, which require complex paracrine mediated growth factor influences for mitogenic and cellular differentiation activity. Additional growth factors include transforming growth factor (TGF), platelet derived angiogenesis factor (PDAF), platelet derived epidermal growth factor (PDEGF), fibroblast growth factor (FGF), keratinocyte growth factor (KGF), insulin like growth factor (IL-GF) and many others which are known to possess different properties mostly through mitogenic and cell differentiating activity mediated by cellular transduction pathways.

The identification of these growth factors within the wound-healing cascade has led to the development of strategies for growth hormone replacement. Beclermin (Regranex®) was the first recombinant PDGF approved for the treatment of diabetic wounds, available in gel form for topical application. Additional growth factors for recombinant DNA application include TGF, which is currently being tested for approval. Studies, however, have shown that a single growth factor applied into a wound is not as effective as multiple growth factors. This is not surprising, as the wound healing cascade requires multiple growth factors for different stimulatory and inhibitory functions at different phases over long periods of time within the different stages of the wound-healing cascade. From prior research on surgical and non-surgical wounds it became apparent from a physiological perspective that the goal of treatment is combination therapies utilizing a multitude of growth factors known to be instrumental in tissue proliferation and remodeling. This understanding has led to the need for bio-tissue engineering strategies, which can provide simultaneous multiple growth factor therapies.

Bio-tissue engineering strategies have led to the development of human skin equivalents (HSE). In addition to the pig gut epithelium (OASIS), human fibroblasts have been cultured resulting in connective tissue from fetal foreskin (Dermagraft, Apligraft). Research has shown that these autogenic and allogenic tissues produce a variety of growth factors and have been demonstrated to be effective in wound healing. In addition to these tissues (fibroblasts) have been shown to migrate and colonize within the wound bed as long as 6 months after its application. These treatment strategies are currently approved for non-healing ulcers involving the lower extremities.

PRP technology was developed in the early 1980's through cell saver technology for surgical applications. Large volume autologous blood sequestration was used to concentrate platelets and white cells during surgical procedures for the immediate application into the surgical field for the purpose of providing tissue sealants, hemostasis and improve surgical healing. This was based upon research, which demonstrated that platelets contain a rich source of multiple growth factors within the alpha-granules, which can be activated and subsequently secreted after activation with thrombin. Platelet counts in excess of 1 million lead to improved surgical hemostasis and wound healing. As a result, further technological advancements have led to the development of small tabletop centrifuges requiring smaller blood volumes while maintaining high acquisition counts of platelets, often in excess of 1.2 million. Most procedures now are accomplished in approximately 1 hour with kits that are completely disposable eliminating concerns of blood handling, out of facility manipulation and infectious disease related issues.

The PRP procedure is surgeon directed after proper in-service with the assistance of a certified perfusionist trained in pheresis techniques. The procedure is affected by drawing 50 ml of whole blood. The blood is processed in a FDA cleared centrifuge for sequestration of the buffy-coat, thereby pheresing the platelets along with blood tissue components including white cells and fibrinogen. The PRP is then activated with CaCL and thrombin resulting in a gelatinous solid, which can be shaped by the surgeon depending upon the anatomical requirements of the surgical site. The surgical site, when determined appropriate by the surgeon, applies PRP as a solid, gel (often mixed with autologous bone) or a thin layer sprayed over dura depending upon the anatomical region of interest. Surgical applications for PRP have been successfully used in trans-sphenoidal hypophysectomy, pituitary tumor, dural rents/tethered cords, LP shunt, lumbar laminectomies, dural wound repair and sealant, CABG, valve surgery, lung surgery, vein harvest site, bronchopleural fistula, mediastinum sealant, aortic aneurysms, carotid endarterectomy, vascular bypass grafts, spinal fusion, total joint arthroplasty, non-union fracture, internal fixation, hepatic lobectomy, pancreatectomy, splenic surgery, enterocutaneous fistulas, mastectomy, axillary dissection, heminephrectomy, retroperitoneal tumor resection, radical retropubic prostatectomy, thyroidectomy, radical neck dissection, parotidectomy, acoustic neuroma, craniofacial reconstruction, facial nerve reconstruction, esophagocutaneous fistula, elimination of surgical drains, LeFort procedures, mandibular reconstruction, particulate bone grafts, nasoalveolar repair, extraction sockets, sinus lifts, face lifts, blepharoplasty, brow lifts, abdominoplasty, split and full thickness skin grafts.

Given the effective and safe use of PRP within surgical applications it became clear that PRP could be used safely for post-op surgical wound dehiscence in an outpatient wound setting.

This was particularly true of diabetic patients who are immunocompromized and experience a higher rate of surgical complications. These same patients are also considered high risk for traditional surgical allografts prompting the need to explore nonsurgical treatment strategies to optimize wound healing by secondary intention. PRP has been further refined to possess structural and functional properties as close as possible to those of natural soft tissue and epidermis. The increasing attention to bio-tissue engineering is based, in part, on the graft's function of compensating for tissue loss by acting as an occlusive dressing, as a three dimensional volumetric soft connective tissue replacement, and as a stimulus for healing. Bio-engineered PRP tissue provides a matrix for cell migration and delivers multiple growth factors to the wound bed. Because PRP contains autologous living cells, they are able to deliver a program of healing to the wound that may not be achieved with single growth factors alone.

This was also true of non-diabetic immunocompromized wounds such as patients receiving immunosuppresant therapy for autoimmune disease as well as patients with prior history of cancer who had undergone prior radiation therapy and chemotherapy. The further refinement of cell saver technology now has allowed PRP to be applied safely within the out patient setting by appropriately trained personal (mostly perfusionist) resulting in lower costs and shorter hospital stays. Additional benefits of PRP include: a non-invasive (other than phlebotomy) painless procedure, no requirement for anesthesia, and outpatient (office/treatment room) performance. The positive experience with diabetic surgical wound cases led to the use of PRP for patients with non-surgical diabetic wounds and non-diabetic immunocompromized wounds, mostly involving the lower extremity. PRP is now being used effectively and safely when primary wound treatment strategies are shown to fail after 60 to 90 days of treatment.

In the outpatient wound care setting a physician trained in wound care with the assistance of a perfusionist can apply PRP in approximately one hour without storage of any blood products. The autologous platelet graft is a physician directed, point of care procedure wherein approximately 50 cc of whole blood is drawn for further sequestration of the buffy coat. During centrifugation, the physician prepares the wound site by sharp debridement of the interior wound tissue exposing an open and receptive vascular bed. At this point the harvested cellular buffy coat is combined with thrombin and CaCl for platelet activation resulting in the construction of a gelatinous material (approximately 5cc – 10cc sufficient for most wounds) that is a malleable graft material. The graft material can be shaped specifically by the physician to meet the 3 dimensional volumetric wound void, which is often irregular in shape resulting in a graft which conforms exactly to the wound dimensions. At this point the graft can be considered as a autologous living tissue free graft as living cells further concentrated are removed from one part of the body and immediately implanted or attached to another location on the same individual. The tissue graft constructed in this manner has a semi-solid physical integrity much like bilaminant skin grafts.

Prior studies with HSE have proven that these cells migrate into and colonize within the wound bed and remain for up to 6 months. This physical integrity allows the molding, cutting, sizing and translocation to an open and receptive wound or incision bed. Although the graft inherently adheres to the surrounding tissue bed the graft material is further secured as determined appropriate by the physician including special op-site dressings or tension sutures. The resulting autologous graft not only serves as a rich source of growth factor therapy but also

provides a matrix medium for cell migration, granulation tissue formation and epithelial wound contracture in addition to serving as a non-disturbed wound patch. The primary occlusive closure dressing will normally remain in place for 5 to 10 days as directed by the physician with appropriate follow up care at the wound management program. The absence of graft-associated infections is explained by the presence of concentrated leukocytes (average of 5 fold over baseline), which are also within the graft matrix.

When given a choice, patients most often prefer autologous PRP soft tissue and bone grafts over autogenic and allogenic graft technology due to the concern of the possibility of infectious disease and tissue rejection. The autologous graft represents a safe and effective alternative to allogenic human skin equivalents and nonhuman derived tissue epithelium eliminating infectious disease concerns.

Indications and protocols for the use of PRP in the surgical setting are in keeping with the surgical team and procedures as directed by the hospital and blood handling procedure protocols. Protocols in the out patient setting are as follows:

Patient Selection Criteria

PRP is indicated for use in the treatment of diabetic and non-diabetic immunocompromized wounds when ALL of the following criteria are met and documented:

- The patient has documented Type I or Type II diabetes mellitus and or is immunocompromized from prior chemotherapy, radiation therapy and or is receiving immunosuppressants for the treatment of autoimmune disease;

- The treatment is specific to clinically non-infected full thickness wounds that have been present for a minimum of 4 weeks;

- The wound must be free of eschar, obvious necrotic tissue, or cellulitus in any part of the wound, as this will interfere with the proper adherence of the graft and decrease therapeutic effectiveness;

- The wound must extend through the dermis and may involve tendon, muscle or bone exposure;

- The wound must have failed to respond to intensive conventional wound treatment for at least 4 weeks duration to include: serial physician evaluations, appropriate biomechanical offloading, adequate control of serum glucose, avoidance of known toxic inhibitors (hydrogen peroxide and iodine solution), nutritional assessment, treatment of colonized infections, proper wound dressings achieving a moist and sterile wound environment, frequent debridement and the correction of underlying metabolic processes (CHF, COPD, renal disease, PVD) and tobacco cessation;

- The patient must have adequate large vessel arterial blood supply to support tissue growth (arterial Doppler studies, angiography, peripheral vascular consultation, etc.);

- The patients is competent or has appropriate support system required to participate in follow-up care associated with the treatment of the wound.

Prior to PRP application, it is expected that the medical and procedural documentation will contain evidence that the intensive conventional ulcer treatment measures have failed to achieve an acceptable rate of healing, herein defined as at least a 20% decrease in wound volume as measured by length (longest dimension) times width (widest dimension) times depth (deepest point) after 4 weeks of intensive conventional wound management.

Additionally, the frequency of the graft application for wounds should be consistent with each patient's specific medical history and demonstrate response to treatment. The recommended frequency is twice monthly not to be reapplied in under 14 days until reassessment adequately demonstrates a positive clinical response as measured by a decrease in wound volume or evidence of new tissue formation with digital photography. No significant response to grafting should prompt the physician to explore other potential inhibitors of wound healing before further grafting is applied. In severe cases as determined by the physician, PRP grafting can be applied weekly during the intitial phase of treatment for wounds, which are at high risk for amputation, not to exceed 4 weekly treatments, then followed by twice monthly applications if indicated.

Contraindications for PRP

Patients who are considered to be candidates for PRP grafting must undergo hematological evaluation by the physician, which includes a review of past medical history and CBC to screen those who have blood dyscrasias or clinical evidence of platelet dysfunction.

Contraindications include:

- Unexplained anemia where Hg is < 12.5
- Thrombocytopenia < 100,000
- Diagnosed and treated anemia Hg<10.0
- Patients who have metastatic disease
- Presence of tumor in the wound bed
- History of platelet dysfunction
- Active wound infection and sepsis requiring systemic antibiotics
- Patients with religious beliefs that prevent the use of blood
- Patients with poor prognosis associated with other disease processes
- Patients with bovine sensitivity

PRP represents a safe and effective autologous treatment alternative for surgical and wound applications when physician directed with the support of certified perfusionists trained in proper transfusion and pheresis techniques. Given the absence of infectious disease concerns, the absence of tissue rejections, as well as the absence of "out of facility" handling of tissue for transplantation, PRP should be considered as first line therapy before autogenic and or allogenic sources of tissue transplantation. Patients who have contraindications for PRP can be considered for autogenic or allogenic HSE's and or other related approved treatment strategies.

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