Platelet-rich Plasma: Properties and Clinical Applications

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ABSTRACT

Platelet-rich plasma (PRP) is an autologous product derived from whole blood through the process of gradient density centrifugation. Autologous PRP has been shown to be safe and effective in promoting the natural processes of wound healing, soft tissue reconstruction, and bone reconstruction and augmentation. The potential value of PRP lies in its ability to incorporate high concentrations of platelet-derived growth factors, as well as fibrin, into the graft mixture. Recently published studies have demonstrated beneficial results with PRP used in a broad range of clinical healing applications. PRP has been shown to increase the rate of bone maturation and to improve bone density when added to small bony defects, or to larger defects in combination with grafting material. Moreover, PRP can be exogenously applied to soft tissues to promote wound healing and tissue sealing. In patients undergoing certain surgical procedures, perioperative use of PRP may decrease the length of hospitalization and the need for allogeneic blood products. PRP is a promising biotechnology that is fueling growing interest in tissue engineering and cellular therapeutics.

I. INTRODUCTION

Platelet-rich plasma (PRP) is an autologous product that concentrates a large number of platelets in a small volume of plasma.[1,2] PRP functions as a fibrin tissue adhesive with hemostatic and tissue sealing properties, but it differs from fibrin glue and other platelet-poor tissue adhesives because its platelets provide a unique ability to promote wound healing and enhance osteogenesis.

PRP provides an immediate surgical hemostatic agent that is biocompatible, safe, and effective. PRP accelerates endothelial, epithelial, and epidermal regeneration, stimulates angiogenesis, enhances collagen synthesis, promotes soft tissue healing, decreases dermal scarring, enhances the hemostatic response to injury, and reverses the inhibition of wound healing caused by glucocorticoids. The high leukocyte concentration of PRP has an added antimicrobial effect. Since PRP is an autologous blood product, it carries no risk of transmitting infectious disease.

PRP has an extremely broad range of clinical healing applications in head and neck surgery, otolaryngology, cardiovascular surgery, burns and wound healing, oral and maxillofacial surgery, cosmetic surgery, and periodontics (Table 1). In addition to its effectiveness for patients with chronic non-healing wounds, it has also been used as an antiangiogenic agent and as a carrier for growth factors.

In surgical settings, PRP decreases the frequency of intraoperative and postoperative bleeding at donor and recipient sites, accelerates soft-tissue healing, supports the initial stability of grafted tissue at recipient sites as a result of its cohesive and adhesive nature, promotes rapid vascularization of healing tissue by delivering growth factors and, when used in combination with bone replacement materials, induces regeneration.

PRP vs. Fibrin Glue

Use of PRP involves taking a sample of a patient's blood preoperatively, concentrating autologous platelets by centrifugation, and after activating the platelets with thrombin and calcium, applying the resultant gel to the surgical site. This technique produces a blood clot in which platelets predominate in nearly a reverse ratio to red blood cells compared with a natural clot. Surgical sites enhanced with PRP heal at rates two to three times those of untreated surgical sites.

PRP must be distinguished from fibrin glues or sealants, which have been used for many years as a surgical adjunct to promote local hemostasis at incision sites. The important difference is the high concentration of platelets and the normal concentration of fibrinogen in PRP, whereas autologous fibrin glues or sealants can be created from *platelet-poor plasma* and consist primarily

TABLE 1. MISCELLANEOUS CLINICAL APPLICATIONS FOR PRP.

Neurosurgery
Pituitary tumor removal
Skull base tumor resection
Intradural procedures involving tumor or release of tethered cords
Dural tumors
Acoustic neuroma excisions (dura tears during laminectomy)
Oral and Maxillofacial Surgery
Mandibular reconstruction
Alveolar cleft repair
Oral-nasal fistulas
Otorhinolaryngology-Head and Neck Surgery
Radical neck dissections
Pectoralis major myocutaneous flaps
Facial fractures
Reconstructions
Cosmetic Surgery
Full and split-thickness skin grafts donor sites and recipient sites
Skin flaps
Bone grafts
Metal implants
Tissue expansion
Aesthetic Surgery (Face Lifts, liposuction, etc)
Augmentation & reduction mammoplasty
Reconstructions
Urology
Radical retro-pubic prostatectomy, & retroperitoneal lymph node dissections
Periodontal Surgery
Dental implants
Guided Bone Regeneration
Orthopedic/Spinal Surgery
Total Hip Replacement
Total Knee Replacement
Scoliosis Repair
Spinal Fusion
All Open and Internal Reduction Fixation Operations
Hand and Foot Surgery
Bone Graft Surgery
Cardiothoracic Surgery
Sternotomy
Graft Conduit Sites
Esophagogastrectomy
General Surgery
Recurrent Hernia Repair
Anal Fistula
Bariatric Surgery

of fibrinogen. (Commercial fibrin glues are created from pooled homologous human donors.) When PRP combined with thrombin and other activators such as calcium is used as an autologous formulation of fibrin glue, the high concentration of platelets promotes wound healing, bone growth, and tissue sealing.

II. MECHANISMS

Hemostatic Response to Injury

The initial vascular response to injury includes the release of subendothelial factors that attract circulating platelets and activate coagulation proteins. Platelets respond by aggregating at, and adhering to, the site of injury, where they release granules containing serotonin, thromboxane, and adenosine, and initiate coagulation and the formation of fibrin. Local production of thrombin enhances activation of platelets and the subsequent formation of a hemostatic plug which minimizes further bleeding. Production of thrombin and activation of platelets also initiate the process of wound healing via thrombin-dependent cell activation and platelet-dependent angiogenesis.[3]

PRP mimics the last step of the coagulation cascade, the formation of a fibrin clot. In vivo, the development of a primary hemostatic plug begins with the activation of platelet membrane receptors through which the adhesive macromolecules von Willebrand factor and fibrinogen anchor platelets to the vessel wall and link them to each other. A secondary hemostatic plug composed of platelets enmeshed in fibrin, results from the action of thrombin, which is essential for the formation of fibrin

TABLE 2. GROWTH FACTORS IN PLATELETS.

Growth Factor	Primary Functions
Epidermal growth factor	Regulation of cell proliferation, differentiation, and survival
Insulin-like growth factor	Key regulator of cell metabolism and growth Stimulates proliferation and differentiation functions in osteoblasts
Platelet-derived growth factor	Major mitogen for connective tissue cells and certain other cell types. Promotes the synthesis of collagen and structural proteins
Transforming growth factor (ie, alpha, beta)	Regulation of cell proliferation, differentiation, and apoptosis Induction of intimal thickening
Vascular endothelial growth factor	Regulation of angiogenesis

and the activation of coagulation factors V and VIII. The balance of all components—vessel wall, platelets, adhesive proteins, coagulation factors, and regulatory mechanisms—determines the effectiveness of the hemostatic plug in maintaining the structural and functional integrity of the vessel.

Growth Factors

PRP exerts its beneficial effects via the degranulation of the alpha granules in platelets that contain growth factors believed to be important in early wound healing (Table 2). When the platelets in PRP are activated by thrombin, they release growth factors and other substances that serve to accelerate the wound-healing process by increasing cellular proliferation, matrix formation, osteoid production, connective tissue healing, angiogenesis, and collagen synthesis.

The active secretion of these growth factors begins within minutes of the start of the coagulation sequence, and more than 90% are secreted during the first hour. After this initial burst, the platelets synthesize and secrete additional growth factors for the remaining 7 days of their viability. Macrophages then arrive due to the vascular in-growth stimulated by the platelets and regulate wound-healing by secreting some of the same growth factors plus additional ones. The rate of wound healing is determined by the number of platelets in the blood clot within the graft or wound, and PRP increases that initial number.

Preparation

Numerous techniques have been described for the immediate preoperative preparation of autologous PRP, but most are variations on a standard theme. Blood is drawn from the patient and fractionated using centrifugation. The platelets are concentrated in the platelet rich plasma at levels generally 6 to 8 times the baseline levels. The resultant PRP is stored at room temperature until needed, at which time 10,000 units of powdered bovine thrombin is mixed with 10% calcium chloride. Next, the PRP is drawn into a 10ml syringe. The thrombin/calcium-chloride mixture then is aspirated into a 1 ml syringe and both syringes are mounted in a mixing applicator. At the tip of the applicator, the two preparations are mixed to activate the PRP. Within 5 to 30 seconds, a gel is formed as the citrate is neutralized and the thrombin activates polymerization of the fibrin and degranulation of the platelets. The gel then is inserted into the surgical field as needed.

Most current methods of PRP preparation use calcium and bovine thrombin to initiate formation of PRP gel. The use of bovine thrombin has unfortunately been associated with the development of antibodies to human clotting factors V, XI, and thrombin, resulting in a risk of potentially life-threatening coagulopathies. Consequently, there is a growing interest in identifying alternative agents for activation of PRP, such as autologous human thrombin or synthetic peptides such as thrombin receptor agonist peptide-6.[4]

Several commercial systems are available for preparing PRP, including the Cobe Angel Whole Blood Separation System which also can produce fibrin glue (Cobe Cardiovascular, Inc., Arvada, Colorado) and the Sequire Platelet Concentrating System (PPAI Medical, Fort Myers, Florida). Most commercial PRP preparation

systems are available for office use by dental practitioners, podiatrists and wound care physicians. In comparison with previous methods that employed autotransfusion devices, current automated systems have shorter preparation times and require substantially less blood volume.

Clinically, PRP is routinely combined with bone substitutes during oral and maxillofacial surgical procedures. These include BioOss, an inorganic bovine bone substitute, AlloGro, demineralized freeze-dried human bone allograft, and 45S5 BioGlass, a melt-derived bioactive glass ceramic.

III. PHYSIOLOGIC EFFECTS

Wound Healing

Human studies have shown that PRP can be advantageously and easily applied in surgery. Man and colleagues used PRP in 20 patients undergoing cosmetic surgery, including face lifts, breast augmentations, breast reductions, and neck lifts. The application of PRP yielded adequate hemostasis if platelet-poor plasma (PPP) was also applied to create a seal to halt bleeding, because PPP contains much higher amounts of fibrinogen. The authors reported that bleeding capillaries were effectively sealed within 3 minutes after application of PRP and PPP. They also noted the added advantage that the use of electrocautery could be minimized, thus decreasing the risk of damage to adjacent nerves. They concluded that PRP offered significant benefits in terms of accelerated wound healing and tissue repair.

Bone Regeneration

Platelets have been shown to stimulate the mitogenic activity of human trabecular bone cells and to increase the proliferation rate of human osteoblast-like cells and stromal stem cells, thus contributing to the regeneration of mineralized tissues. Growth factors released from platelets signal local mesenchymal and epithelial cells to migrate, divide, and increase synthesis of collagen and matrix, thus providing a scaffold that encourages migration of osteoblasts. Growth factors contained in PRP also stimulate chemotaxis, metabolism, and proliferation in osteoblasts and in bone marrow osteoprogenitor cells.[6,7]

Guided bone regeneration is a standard surgical technique employed in implant dentistry to increase the quantity and quality of the host bone in areas of localized alveolar defects. The unpredictability of osseous regenerative procedures with various grafting materials suggests that it would be highly desirable to improve their ability to induce new bone formation (osteoinduction) properties.

In subantral sinus augmentation, the combination of PRP and freeze-dried bone allograft (FDBA) has been shown to improve the rate of bone formation compared with FDBA and resorbable membrane.[8] Biopsy specimens obtained 4.5 to 6 months after the grafting procedure, when implants were being inserted, revealed that sinuses treated with FDBA and PRP had a significantly higher percentage of vital tissue and bone than those treated with FDBA and membrane. Similarly, the relative proportion of vital bone to residual graft particles was significantly greater with PRP.

CLINICAL STUDIES

In addition to PRP's use for reconstruction of soft tissue and bone in facial plastic and reconstructive surgery, a wide variety of applications elsewhere in the body has been reported. However, many reports are anecdotal and few include controls. Despite a large variety of animal studies, the findings are often conflicting, and the studies lack standardization. Conclusions from comparisons between clinical and animal studies must be viewed with caution.

In one of the largest prospective, randomized, clinical trials of PRP, Everts and colleagues randomized 165 patients undergoing total knee arthroplasty to receive autologous PRP and fibrin sealant applied on the wound at the end of surgery vs. standard surgical techniques.[9] Patients in the PRP group had a significantly higher post-operative hemoglobin level (11.3 vs. 8.9 g/dl, respectively), and a decreased need for allogeneic blood products (0.17 vs. 0.52 units, respectively) ($P < 0.001$). The incidences of wound leakage and wound healing disturbance were significantly less ($P < 0.001$) in patients managed with PRP and fibrin sealant, and their hospital stay was decreased by an average of 1.4 days ($P < 0.001$).

PRP has recently been shown to reduce the incidence of sternal infections after cardiac surgery. Trowbridge and colleagues compared a treatment group of 382 patients who received PRP with a control group of 948 who did not. The incidence of superficial infection was significantly lower in the treatment group (0.3% vs. 1.8%, $p < .05$). As for deep sternal wound infections, none were seen in the treatment group, versus 1.5% in the control group.[10]

The beneficial effects of treatment with PRP in patients with chronic cutaneous wounds have been inconsistent.

Margolis et al. reported that diabetic neuropathic foot ulcers treated with PRP were 14–59% more likely to heal than those treated with standard care.[11] The beneficial effects of PRP were greatest in patients with the most severe wounds, i.e., large wounds affecting deeper anatomical structures. In contrast, Senet et al observed no beneficial effects of adjuvant treatment with PRP on wound healing in a randomized, double-blind, placebo-controlled study of 15 patients with chronic venous leg ulcers.[12] Wound fluid growth factor levels were not modified by treatment with PRP.

Contraindications

Treatment with autologous PRP is generally considered safe in appropriately selected patients. Potential candidates for treatment with PRP should undergo a pre-treatment hematologic evaluation to rule out potential coagulopathies and disorders of platelet function. Patients who are anemic and those with thrombocytopenia may be unsuitable candidates for treatment with PRP. Other potential contraindications include hemodynamic instability, severe hypovolemia, unstable angina, sepsis, and anticoagulant or fibrinolytic drug therapy.

CONCLUSIONS

Autologous PRP is a relatively new biotechnology that has shown promise in the stimulation and acceleration of soft-tissue and bone healing. The efficacy of this treatment lies in the local delivery of a wide range of growth factors and proteins, mimicking and supporting physiologic wound healing and reparative tissue processes. Consequently, the application of PRP has been extended to many different fields, including orthopedics, sports injuries, dental and periodontal surgery, and cosmetic, plastic, cardiovascular, general and maxillofacial surgery.

Few well-designed scientific studies of the clinical use of PRP are available, and the optimal roles of PRP remain undefined. The exact mechanisms of action of the many components of PRP are not fully understood, and the ideal ratios of these components are unknown. In some circumstances, the costs of implementing this promising technology must be weighed against its benefits, and well-designed controlled clinical studies are needed to provide clear evidence of the capacity of PRP to improve patient outcomes.

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