Current Applications of Platelet Gels in Facial Plastic Surgery

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ABSTRACT

The response of living tissue to injury is a central component in the planning of all surgical procedures. The wound-healing process is typically divided into three phases (inflammatory, proliferative, and remodeling) and is a complex process in which a multitude of cellular and humoral components interact to restore a wound defect. Platelets and their released cytokines and growth factors are pivotal in the modulation of this entire process. Although several techniques may be used to achieve hemostasis after initial injury, few initiate and actually accelerate tissue regeneration. Both platelet gel and fibrin glue are effective hemostatic agents. Platelet gels, unlike fibrin glue, have a high concentration of platelets that release the bioactive proteins and growth factors necessary to initiate and accelerate tissue repair and regeneration. In particular, two growth factors that play a major role in platelet gels are platelet-derived growth factor, a powerful chemoattractant, and transforming growth factor β, which significantly increases and stimulates the deposition of extracellular matrix. In creating a platelet gel, autologous blood is centrifuged to produce a concentrate high in both platelets and plasma. This concentrate can be applied to wounds, providing hemostasis, adhesion, and enhanced wound healing. Recent techniques for the autologous concentrating process have been streamlined, and now platelet gels are clinically accessible to most physicians. Platelet gels have global applications in surgery and are especially useful for the soft tissue and bony reconstructions encountered in facial plastic and reconstructive surgery. In these applications, their use has been associated with a decrease in operative time, necessity for drains and pressure dressings, and incidence of complications. When applied to bony reconstruction it provides adhesion for the consolidation of cancellous bone and comminuted fracture segments.

KEYWORDS: Blood products, platelet gels, tissue sealants, fibrin glue

BASIC SCIENCE OF WOUND HEALING

Wound healing is a very intricate process involving the complex interplay of numerous humoral factors and cells. It is divided into three overlapping stages: inflammatory, proliferative, and remodeling. The inflammatory phase begins with tissue injury, which leads to platelet aggregation and release of platelet growth factors, cytokines, and hemostatic factors. Both intrinsic and/or extrinsic pathways mediate the clotting cascade, a central component of the early inflammatory phase (Fig. 1). The intrinsic pathway is activated when, in the presence of kininogen and prekallokrenin, factor XII (Hageman factor) comes in contact with collagen and activates factor XI. Activated factor XI in turn activates factor IX, which, in the presence of activated factor VIII and calcium, activates factor X. Meanwhile, in the extrinsic pathway, tissue damage results in the release of thromboplastin (formed from phospholipids and glycoproteins),

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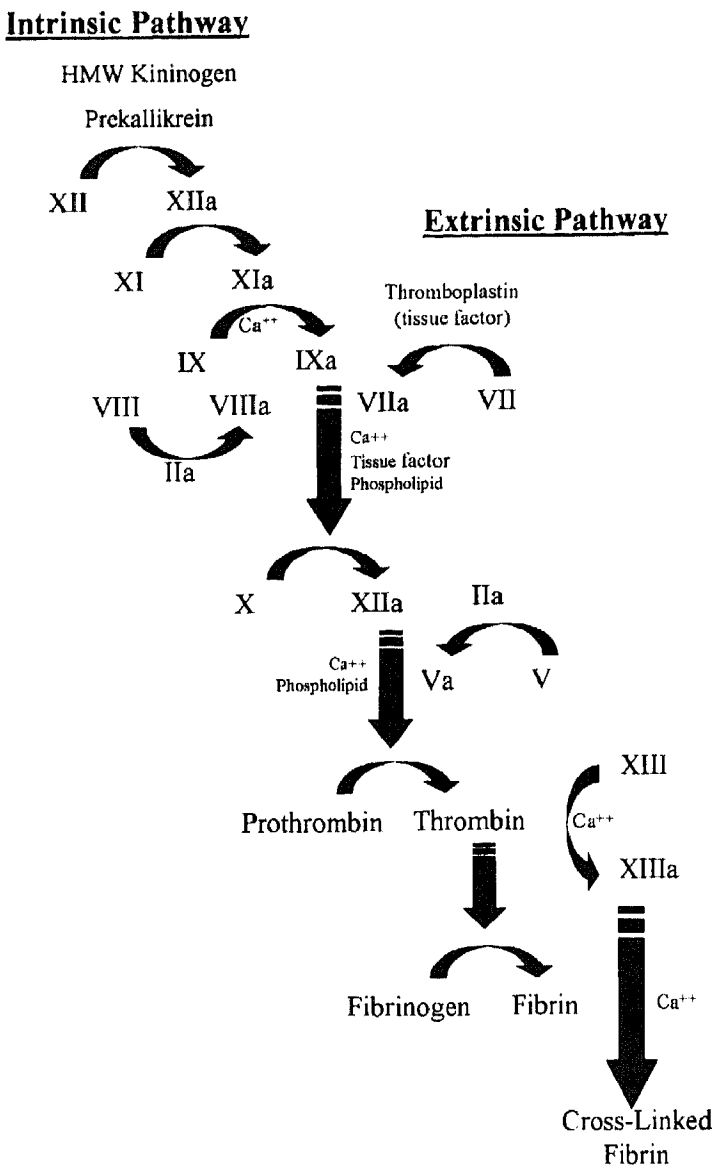

Figure 1 Coagulation pathway. See text for details.

which activates factor VII and subsequently factor X. In the common pathway, factors X and V interact with calcium and convert prothrombin to thrombin. Thrombin converts fibrinogen to fibrin monomers and activates factor XIII, which then polymerizes the fibrin monomers by cross-linking them into an organized clot. This structural matrix allows monocytes, keratinocytes, and fibroblasts to adhere to the wound area.

Platelets and other inflammatory cells release a number of cytokines and growth factors. The thromboxane and serotonin released by platelets cause vasoconstriction and consequently aid in hemostasis by preventing the dissipation of local tissue factors from the injury site. At the same time, other areas of the wound are under the influence of histamine, also released by platelets, which increases vascular permeability, allowing entry of additional cells and factors from blood. Attracted by local factors, polymorphonuclear leukocytes and monocytes migrate out of blood vessels to the site of injury. The monocytes differentiate into macrophages and along with neutrophils kill and phagotize bacteria and debris. Thereafter, endothelial cells begin to proliferate and fibroblasts migrate to the injury site, marking the beginning of the proliferative phase.

During the proliferative phase macrophages remove debris and bacteria, whereas fibroblasts synthesize a ground substance. Under the influence of chemotactic growth factors, migrating endothelial cells create new blood vessels in the process known as angiogenesis. The restored blood flow brings necessary nutrients and oxygen for optimal wound healing. Soon more fibroblasts accumulate and initiate the deposition of an extracellular matrix consisting of mainly mucopolysaccharides,

collagen, and elastin. Epithelialization is also accomplished in this phase, commencing from the edges of the wound. The resulting scar at the end of the proliferative phase is then further altered with respect to both its ground tissue matrix and collagen fibers in the remodeling phase. In this phase, a mature scar is produced as collagen lysis reaches equilibrium with collagen synthesis and the collagen fibers are realigned for optimal strength. The process of remodeling can take up to 2 years and results in a scar that usually has approximately 80% the strength of normal skin.

To expedite the process of wound healing and minimize edema and scarring, surgeons try to obtain hemostasis and reapproximate the edges of the wound as close to the preinjury state as possible. Traditionally this has been accomplished by mechanical methods such as sutures that physically hold the edges of the wound together while an adhesion is formed. More recently tissue glues have been introduced for this purpose.

TISSUE SEALANTS AND GLUES

Synthetic Sealants

Cyanoacrylates, which were first described in 1949, are tissue adhesives that polymerize once in contact with fluids, solids, or tissues. Earlier shorter-chain monomers caused inflammatory reactions and therefore were abandoned in favor of longer-chain monomers such as butylcyanoacrylate that had minimal inflammatory response. However, this family of cyanoacrylates was brittle and lacked tensile strength.

These shortcomings were addressed by the next generation of cyanoacrylates, the octylcyanoacrylates. Octylcyanoacrylates, unlike its predecessors, consist of a combination of a monomer and plasticizers that polymerize to form a flexible and strong bond. Currently, octylcyanoacrylate has been approved for topical/external use as a wound sealant.[1] This sealant offers the benefits of good wound edge adhesion with significant time saving over the use of sutures and avoids issues of suture removal and suture track scarring.[1] In addition to providing physical adhesion, certain biological products contain additional elements that promote rapid wound healing. Among these products are fibrin glue and platelet gels.

Fibrin Glue

Fibrin's adhesive properties were first discovered by Bergel in 1909, and the application of a fibrinogen derivative in liver and cerebral hemorrhage was first described by Grey in 1915.[2,3] This was followed by the work of Cronkite et al. and Tidrick and Warner, who combined fibrinogen and thrombin to successfully fixate skin grafts.[4,5] However, it was not until 1970, when it was possible to produce high concentrations of fibrinogen, that the use of fibrin-based tissue adhesives or glues became a reality.

Fibrin glue essentially involves the making of concentrated fibrinogen in the presence of factor XIII (fibrin stabilizing factor) and pooled plasma proteins (fibronectin and cold insoluble globulin). This is then combined with thrombin, calcium chloride, and one of three fibrinolysis inhibitors (tranexamic acid, E-amino caproic acid, and aprotinin, of which aprotinin is the most potent). The thrombin cleaves fibrinogen to fibrin and activates factor XIII, which cross-links the fibrin and forms a clot matrix. Fibrinolysis inhibitors inhibit plasmin degradation of the clot.[6] Fibronectin anchors the matrix components to the site of injury and the resulting fibrin cross-linked matrix provides a three-dimensional scaffolding into which undifferentiated cells, such as fibroblasts, can migrate and then proliferate.

Fibrinogen can be obtained from a number of sources, including pooled-donor cryoprecipitate, single-donor cryoprecipitate, or autologous plasma. Due to the possible risk of viral transmission from the multidonor product, the FDA ruled against it in 1978.[7] Since then, there has been one reported case of HIV transmission from the use of a homologous product.[8] This led to the development of both single-donor and autologous cryoprecipitated fibrinogen preparation processes that used multiple freeze/thaw cycles to concentrate the fibrinogen.[9] Although this process produced concentrated fibrinogen that was usable for up to 1 year, the process required several days to complete, making it cumbersome and clinically impractical.

Currently, the formation of most tissue glues involves two steps. First, the patient's whole blood is collected and centrifuged into its plasma and cellular components. The plasma is then drawn up into a syringe and, in a second step, mixed with bovine collagen and thrombin, which act as platelet activators and convert the patient's plasma fibrinogen to fibrin, respectively. However, the quantity and quality of some commercial preparations may produce such a dense architecture that angiogenesis and overall healing is inhibited.[10,11] In addition, the fibrin glue matrix is considered bioactively passive in that it does not possess a mechanism to actively recruit undifferentiated cells into its scaffolding. Although these characteristics do not affect the fibrin clot's hemostatic properties, they can result in delayed and defective tissue repair.

Platelet Gels

Recently, in response to these concerns, platelet gels were developed using a new process, differential centrifugation, which can rapidly concentrate autologous platelets and fibrinogen from whole blood. In this pro-

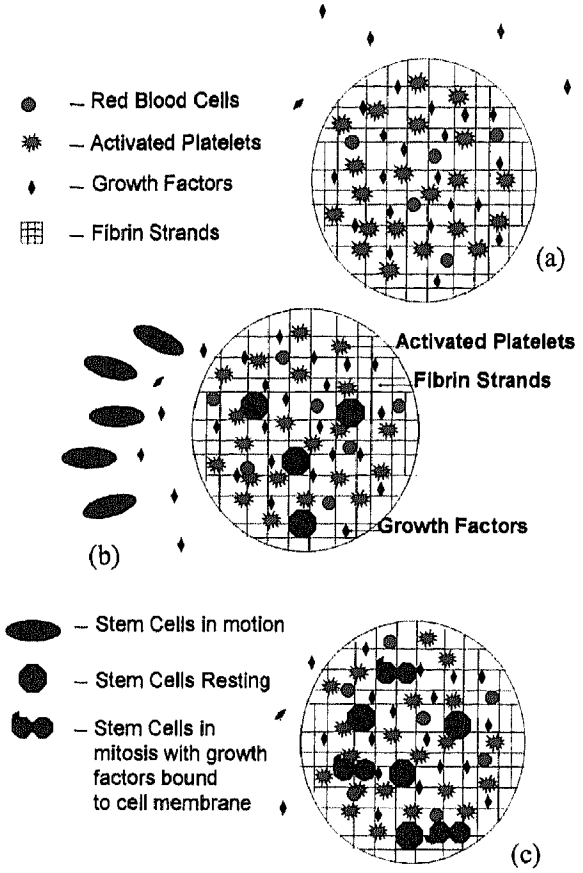

Figure 2 Schematic representation of cellular components involved in platelet gels. (A) Formation of platelet-fibrin matrix and release of growth factors from platelets. (B) Chemoattraction of stem cells into bioactive matrix, under the influence of platelet-released growth factors. (C) Cellular elements in an evolving active platelet gel matrix.

cess whole blood is centrifuged, and the platelet and fibrinogen rich plasma component are harvested.[12,13]

Platelet gels differ from fibrin glue in that they contain a high concentration of platelets that markedly improve the adhesive properties and the wound-healing characteristics when compared with fibrin glue alone. It has been shown that 55% of the clot strength is due to the platelets and 45% is due to the fibrin strands.[14] Thus, the addition of platelets, which bind to both one another and to the cross-linked fibrin strands, markedly improves overall clot strength. However, because the fibrin strands in platelet gel are not increased above normal levels, the matrix structure that is formed has the same open architecture of a typical blood clot and facilitates new capillary in-growth.

Additionally, platelet gels form a bioactive matrix (Fig. 2A) resulting from the high concentration of platelets that release multiple growth factors when activated. These growth factors affect tissue regeneration in two ways. First, the growth factors actively attract undifferentiated cells into the matrix (Fig. 2B) where these 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 (Fig. 2C).[5,15]

In addition to growth factors, platelet gels contain 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 also produce signaling proteins that attract white blood cells. Two of the more important factors

Table 1 Table of Biological Activity of Key Proteins and Growth Factors Required in Wound Healing

Protein	Biological Activity	Fibrin Glue Clots	Platelet Gel
Fibrinogen	Promotes hemostasis, provides scaffolding for undifferentiated cell migration	Yes	Yes
Adhesion molecules (Fibronectin, SCF, vitronectin)	Facilitate intercellular binding and communication	No	Yes
Platelets	Promote hemostasis; initiate wound-healing cascade	No	Yes
Platelet protein (IL-1b)	Signals lining cells of damaged vessels to display receptors for macrophages	No	Yes
Platelet-derived growth factor β	Initiate connective tissue healing; increase mitogenesis, angiogenesis, and macrophage activation	No	Yes
Transforming growth factor beta	Increases the chemotaxis and mitogenesis of osteoblast precursors; stimulates osteoblast deposition of the collagen matrix of wound healing and bone regeneration	No	Yes
Epidermal growth factors	Induce epithelial development and promote angiogenesis	No	Yes
Vascular endothelial growth factors	Contain potent angiogenic, mitogenic, and vascular permeability-enhancing activities specific for endothelial cells	No	Yes

are platelet-derived growth factor (PDGF) and transforming growth factor β1 (TGF-β1). PDGF is a potent chemoattractant and mitogen for fibroblasts, monocytes, and macrophages. It also activates collagenase, which fosters remodeling of collagen in the latter stages of wound healing; PDGF is also thought to play a role in neointimal hyperplasia. TGF-β stimulates collagen, proteoglycan, elastin, and fibronectin synthesis and reduces the expression of collagen and plasmin activator.[6,16] In addition, the platelets release a myriad of other factors that have hemostatic as well as wound-healing enhancement capabilities. The biological functions of several key proteins are listed in Table 1.

There is one caveat. Regardless of the method for making autologous platelet concentrate, to achieve a bioactive matrix with a platelet gel clot, it is important that the platelet concentrate contains viable platelets because only viable platelets release the key growth proteins.

TECHNIQUE

There are a number of different processes described in the literature for obtaining platelet gels, all of which involve differential centrifugation of whole blood obtained prior to any surgical incisions. This is important because any incision or wound made prior to blood collection activates the patient's platelets and coagulation system and decreases the amount of these essential components in the whole blood obtained thereafter.

A number of centrifugation devices have been described for use in the preparation of platelet-rich plasma (PRP) used for platelet gels and platelet-poor plasma (PPP) used for fibrin glue. These include the Medtronic Electromedic, Elmd-500 Autotransfusion system (Parker, CO),[6] the Plasma Saver device by Haemonetics (Braintree, MA),[12] and the SmartPReP™ by Harvest Technologies Corp. (Novell, MA).[17]

The process used by SmartPReP™ exemplifies the technique and results in the production of both autologous PRP and concentrated fibrinogen (PPP). Prior to the start of the operative procedure, a venipuncture is performed, and 90 to 110 cc of the patient's whole blood is drawn up equally between two 60-cc syringes containing 5 cc of a citrate-based anticoagulant (ACD-A). The content of each syringe is placed in a vial and centrifuged, separating the red blood cells from the plasma. Next, while in the centrifuge, the plasma is siphoned off and then respun, further concentrating the plasma platelets into a pellet. This fully automated process takes approximately 12 minutes. The result is a vial with a pellet consisting of platelets and the supernatant consisting of PPP. Approximately two-thirds (approximately 20 cc per syringe) of the supernatant (PPP) is decanted and can be used for hemostatic purposes. The pellet is resuspended in the remaining supernatant to make the PRP solution (approximately 7 cc per syringe). Both PRP and PPP solutions can then be activated by a solution containing 5000 U of topical bovine thrombin (Gen Trac, Middleton, WI) and 5 cc of 10% calcium chloride solution. The systematic combination and delivery of these two solutions are performed using a 20G dual-cannula applicator tip (Micromedics, Inc., Eagan, MN; Fig. 3). The PPP forms fibrin glue once activated, whereas the PRP produces platelet gel.

The SmartPReP™ process recovers approximately 68% of platelets from whole blood and significantly concentrates the growth factors multiple times, specifically PDGF (600%), TFG-β1 (727%), VEGF (428%), and EGF (550%).[18]

Regardless of the surgical procedure, the application of fibrin glue and platelet gels is fairly constant. During the operative dissection, fibrin glue (PPP) can be sprayed on exposed tissue surfaces for hemostasis. When it is time for closure of the wound, a small quantity of gel can be applied to the undersurface of the flap. A gauze is then rolled along the flap in the direction of the desired vector of lift to spread the gel along the undersurface and milk out any excess.[19] The skin closure can also be sealed with the platelet gel.

The use of platelet gels has been associated with decreased operative times, use of drains and pressure dressings, incidence of hematoma and seroma formation, postoperative edema, and postoperative pain.[17] There are two other advantages of platelet gels. First, because platelet gels contain the final components of the coagulation cascade, their use mitigates the effect of any coagulation defects that may occur during surgery or may have gone undetected preoperatively. Second, because of their strong hemostatic properties, platelet gels minimize the use of cautery and, therefore, reduce the risk of nerve injury.

APPLICATIONS IN SURGERY

Autologous platelet gels have a number of advantages and can be applied to a wide array of surgical procedures. Its general applicability is in part due to its unique wound-healing characteristics of hemostasis, tissue adhesion, growth factors, and cytokines. Reports thus far have demonstrated decreased hematoma formation, seroma formation, postoperative swelling, and healing time.[17]

In facial plastic and reconstructive surgery, the dual advantages of fibrin adhesives as hemostatic agents and as adhesive agents are underscored by their use with rhytidectomy flaps, upper and lower blepheroplasties, brow flaps, skin grafts, bone graft donor sites, bony reconstruction, and sutureless closure of incisions.[19] Bruck, in 1982, reported his experience with the use of fibrin glue in 82 rhytidectomies and noted a decrease in operative time and postoperative swelling and an increase in patient comfort.[20] Similarly, in 1994, Marchac reported his expe-

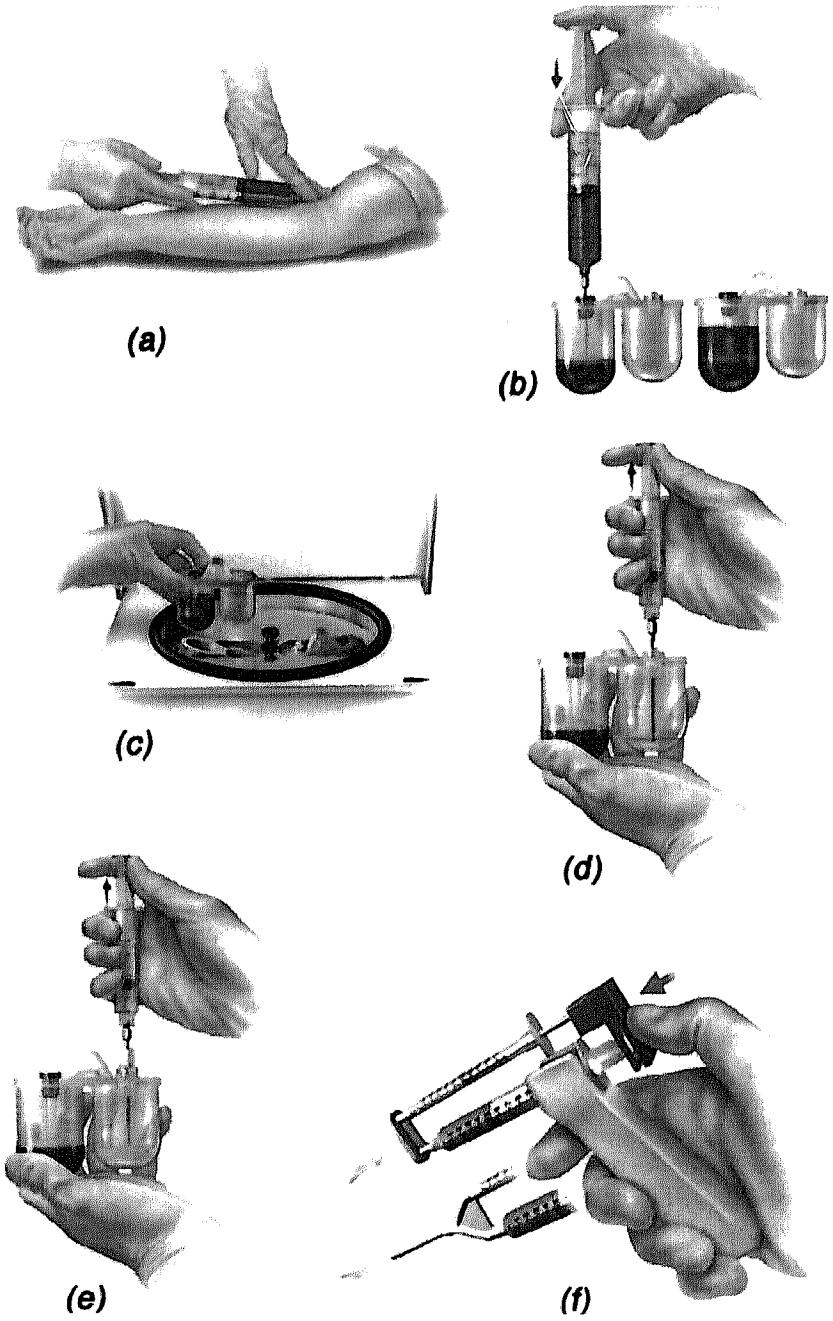

Figure 3 Process used to harvest and apply platelet gels (SmartPRePTM).

rience of the use of fibrin glue in 200 rhytidectomies and observed no change in complications despite the lack of drains and pressure dressing in all cases.[21] Mommaerts, in 1996, observed no difference in scar morphology when comparing 18 patients undergoing blepharoplasty using only fibrin glue for closure with 12 patients using 5–0 nylon for closure.[22] Saltz et al., in 1991, observed increase adherence of split-thickness skin graft, without the use of a bolster, in 82 patients, which included 51 burns.[9]

Fibrin adhesives have been extremely useful in skin graft applications demonstrating improved graft take, especially after debridement of burn eschar where its hemostatic and adhesive qualities are particularly valuable.[16] Other platelet gel applications include dural closures, oral–nasal and oral–antral fistulas repairs, and microvascular and microneural anastomosis.[6,15,23]

In bony reconstruction fibrin glue (PPP) has been used as a hemostatic agent in ilium bone graft donor sites.[6] In mandibular reconstruction, platelet gels (PRP) have been used to reapproximate comminuted bone fragments in complicated fractures, improving the stability of the repair. Platelet gels also promote the adhesion and consolidation of particulate cancellous bone and marrow grafts, making the grafts easier to handle and conform

into allogenic cribs and alloplastic trays.[24] Tayapongsak et al., in 1994, having used fibrin glue in major mandibular reconstruction with autogenous particulate cancellous bone and marrow in 33 patients, demonstrated by radiographs that the remodeling phase occurred 50% sooner than controls (4 vs. 8 weeks).[24] Fibrin adhesives have been also used in a similar fashion in other mandibular reconstructive procedures such as inferior alveolar nerve lateralization, placement of osseointegrated implants, and repair of alveolar clefts. In 1998, Davis and Sandor demonstrated the multiple uses of fibrin glue in maxillofacial sugery with good outcome and no complications, specifically applied to 14 patients with bone and alloplastic fixation, 13 patients with cleft lip and palate repair, and 12 patients with sinus lift procedures for the fixation of bone grafts and repair of torn mucoperiosteal lining.[25] In addition to the obvious mechanical adhesion benefits with bony applications, platelet gels provide a rich physiologic milieu for bone healing due to the presence of growth factors and cytokines in the area of reconstruction.[6]

Other varied surgical applications of platelet gels have been reported. Their use as a biological dressing after laser resurfacing has demonstrated faster healing and decreased erythema.[17] The application of platelet gels to fat grafts obtained by liposuction enhances the fat's longevity when injected for contour augmentation.[17] When platelet gel is used in conjunction with sutures it provides for greater tensile strength of irradiated bowel anastomoses compared with sutures alone.[16] Fibrin glue has also been used with improved outcomes in reduction mammoplasties, abdominoplasties, mastectomies, and axillary node dissections.[16]

SUMMARY

Platelet gels represent the most recent of the line of tissue adhesives that combine the advantages of fibrin glue with the additional benefits of PDGFs and cytokines. Furthermore, a safe autologous form of the product is readily available at the point of use in the operating room with minimal cost and effort. This, coupled with the myriad of uses exemplified by this report, suggests that this technology is likely to see even broader applicability.

However, because platelet gels are an emerging technology much of the present literature is anecdotal. As this technology becomes more mainstream, larger studies will become available to quantify the benefits and clarify the optimal application for this product.

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