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SURGICAL ENDOSCOPY
and Other Interventional Techniques

The use of autologous platelet–leukocyte gels to enhance the healing process in surgery, a review

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Abstract
Background: The therapeutic use of autologously prepared, platelet–leukocyte-enriched gel (PLG) is a relatively new technology for the stimulation and acceleration of soft tissue and bone healing. The effectiveness of this procedure lies in the delivery of a wide range of platelet growth factors mimicking the physiologic wound healing and reparative tissue processes. Despite an increase in PLG applications, the structures and kinetics of this autogenously derived biologic material have not been observed.
Methods: A review of the most recent literature was performed to evaluate the use of PLG in various surgical disciplines.
Results: The review showed that the application of PLG has been extended to various surgical disciplines including orthopedics, cardiac surgery, plastic and maxillofacial surgery, and recently also endoscopic surgery.
Conclusion: This review demonstrates the usefulness of PLG in a wide range of clinical applications for improvement of healing after surgical procedures.

Key words: Growth factors — Leukocytes — Platelet gel — Wound healing

Soft tissue wound healing and bone growth involve physiologic cascades in which cellular and hormonal factors play pivotal roles [1, 2]. Some of these cascade components can be isolated from autologously drawn whole blood. Point-of-care devices can intraoperatively fractionate the autologous blood into platelet-poor plasma, platelet–leukocyte-rich plasma (P-LRP), and red blood cells [3, 4]. The P-LRP fraction, a mixture of concentrated platelets and leukocytes, can be activated by (autologous) thrombin to create a viscous solution known as platelet–leukocyte gel (PLG). This platelet coagulum can be exogenously applied to soft wound tissues, bone, or synthetic bone as a spray or as a solid, clotted, gelatinous mass. The rationale for applying platelet gel is based on the delivery of platelet growth factors to tissues and on the fact that platelet α-granules, found inside the platelets, contain a variety of growth factors [5]. Platelet gel growth factors are peptides that promote cell proliferation, differentiation, chemotaxis, and the migration of various cells involved in both wound healing and bone growth [6, 7].

Recently, numerous P-LRP devices have become available for therapeutic use to stimulate and accelerate soft tissue and bone healing and to control postoperative wound bleeding. The rationale for applying PLG lies in the mimicking and accelerating of physiologic wound healing and reparative tissue processes.

This article provides information on the results of electron microscopic imaging used to evaluate the content of PLG. Furthermore, because the use of PLG is a relatively new per- and/or perioperative biotechnological application, new and additional indications for the use of PLG are defined. New PLG applications are reviewed for different applications including cardiac surgery, general surgery, orthopedics and traumatology, cosmetic surgery, maxillofacial surgery, sports medicine, and endoscopic surgical procedures.

Defining platelet–leukocyte-rich gel

Platelet–leukocyte gel is prepared from a high concentration of platelets acquired from freshly drawn autologous whole blood. In general, this blood is obtained by

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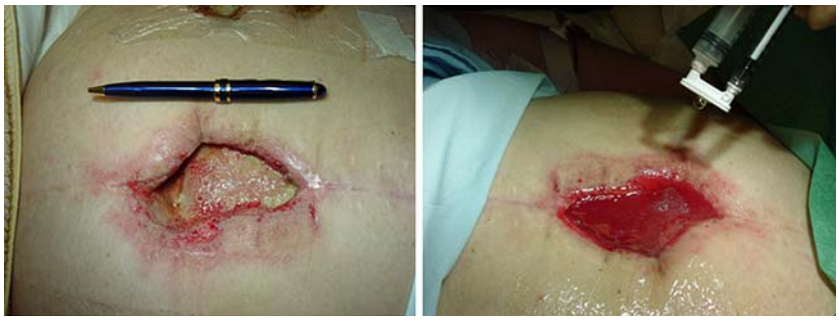

Fig. 1. Using a double-syringe delivery technique, platelet–leucocyte gel is applied on the skin wound of a patient with decubitis ulceration.

point-of-care devices and sequestered into different blood components, namely, P-LRP, platelet-poor plasma, and erythrocyte concentrate [8].

One characteristic of P-LRP is that it comprises a small volume of plasma with fibrinogen, platelets, and leukocytes. Platelets suspended in the P-LRP are in an inactive state and in liquid form. The platelet growth factors are found inside α granules, which are present in the platelet cytoplasm. Platelets become immediately activated because of interaction with thrombin, the most potent platelet activator, and a sticky platelet aggregate is formed. Subsequently, platelet α granules release growth factors into the extracellular environment, where they bind to specific platelet growth factor receptors. After this, through intracellular tissue signaling, a number of pathways are triggered that initiate the healing process.

Besides a high concentration of platelets in PLG, several differentiated and nonactivated leukocytes are present at high levels. In particular, these include neutrophilic granulocytes and monocytes, both known for host defense mechanism actions against bacteria through the action of myeloperoxidase that creates hypochloric acid. The number of platelets in PLG is three to seven times higher than normally found, whereas the white blood cell count is two to four times greater than normal [9–11].

Healing mechanisms of platelet–leukocyte gels

It is generally accepted that platelet growth factors play a central role in the healing process and tissue formation [12]. Wound healing is a well-orchestrated and complex series of events involving cell–cell and cell–matrix interactions, in which platelet growth factors serve as messengers to regulate various processes. Initially, tissue repair begins with platelet clot formation, activation of the coagulation cascade and platelet degranulation, and the release of growth factors. After this release, specific platelet growth factors bind to particular target tyrosine growth factor receptors, which subsequently activate intracellular signal transduction pathways [7, 13].

During the first 2 days of wound healing, an inflammatory process is initiated by migration of neutrophils and subsequently macrophages to the wound site. In turn, activated macrophages release multiple growth factors, including platelet-derived growth factor, transforming growth factors alpha and beta, interleukin-1, and fibroblast growth factor [11]. Angiogenesis and fibroplasia start shortly after day 3, followed by collagen synthesis on days 3 to 5. This process leads to an early increase in wound-breaking strength, which is the most important wound-healing parameter of surgical wounds, followed by epithelialization and the ultimate remodeling process [14].

Some functions of platelet growth factors in tissue repair showed that a controlled sequential appearance is crucial after primary wound closures at the end of surgical procedures for the treatment of bone and cartilage defects as well as muscle and tendon lesions, and for the promotion of synthetic tissue ingrowth during reconstructive surgeries [15].

Based on the actions of the various platelet growth factors during the different stages in the wound healing cascade, the use of autologous PLG to stimulate wound repair is an interesting proposition, although recombinant growth factors have been used to stimulate wound healing. However, as compared with recombinant single growth factor applications, platelet gels have the supreme advantage in that they synergistically induce various growth factors and promote mitogenesis of mesenchymal stem cells at the wound site [16, 17].

Novel platelet–leukocyte gel applications

After the activation of P-LRP with thrombin, a viscous gel with a degree of plasticity is formed that sticks to wound tissues. At this stage, PLG is exogenously applied, using a syringe delivery technique, to surgical wound sites during closure and to soft tissue structures to stimulate tissue regeneration (Fig. 1a and b), , or it is mixed with bone or bone substitutes to accelerate bone healing.

The outcome of multiple studies on the efficacy of PLG treatment have been published [18–20]. Proponents of PLG application refer to improved wound healing and increased bone growth to warrant its use. A reduction in the development of severe postoperative wound infections with the application of PLG during incisional wound closure after a cardiac surgical procedure has been reported [21]. These observations indicate that this is a promising technique, with the result that the delivery of autologous platelet growth factors and vital neutrophilic leukocytes is now gaining more popularity. However, more scientific evidence and data to support the use of PLG in clinical settings are mandatory for progress in the use of these autologous bio-

Fig. 2. Aerosol-controlled laparascopic platelet–leukocyte gel delivery system.

technology procedures to be achieved. Recently, novel applications have emerged in the field of PLG applications and in a variety of surgical disciplines. We reviewed some of these new applications and report on some results of studies that indicate some potentially new directions and clinical applications.

Soft tissue healing and endoscopic applications

Promising results have been obtained for patients with chronic nonhealing (diabetic) wounds after topical PLG application. Margolis et al. [22] demonstrated that the application of PLG was more effective than standard care methods for wound healing, and that this treatment was even more effective for patients with deeper wounds. Furthermore, in our own experience we have encountered improved wound healing with the application of PLG during wound closure after total knee arthroplasty [23].

Soft tissue trauma such as tendon and ligament ruptures and joint capsular injuries, which frequently occur, often require a surgical intervention [24, 25]. It is presumed that surgical repair combined with the application of biologically active PLG should accelerate healing with an improved outcome. Aspenberg and Virchenko [26] showed, in an *in vivo* rat model, that PLG applied to traumatized Achilles tendons increased tensile strength and stiffness by about 30% after the first week. The effect persisted for as long as 3 weeks after the injection, suggesting that the use of PLG in tendon repair improved the physiologic healing process.

Anterior cruciate reconstructive ligament surgery is routinely performed to reconstruct the ligament with an autologous graft. Because the procedure is mainly performed arthroscopically, it is challenging to apply PLG to augment healing. Sanchez et al. [27] reported enhanced healing with fewer complications and improved fixation of the graft within the bone tunnels in a retrospective clinical trial involving 100 patients.

The mechanism of action by which tendon repair is improved with the application of PLG is based on release of vascular endothelial growth factor (VEGF). This growth factor stimulates angiogenesis, leading to an improved blood supply, which is mandatory for the tendon repair process [28]. Furthermore, released platelet growth factors induce a proliferation of tendon cells and stimulate production of VEGF and hepatocyte growth factor, a potent antifibrotic agent. The latter may be of importance in reducing scar formation and fibrosis in newly reconstructed tendon tissue, which may lead to poor outcomes [29].

In the past, fibrin glues have been used to make a sutureless intestine anastomosis and to treat gastrointestinal anastomotic leaks during laparoscopic surgery [30, 31].

Recently, a novel PLG application has emerged for morbidly obese patients undergoing bariatric surgery. Brady et al. [32] used PLG via an endoscopic delivery system (Fig. 2), after a laparoscopic Roux-en Y gastric bypass procedure to avoid hemorrhage, infection, and anastomotic leaks, which may occasionally lead to death. These authors suggest that the use of PLG contributed to an enhanced hemostatic response, accelerated tissue healing, and improved collagen synthesis, thus preventing anastomotic leaks and thereby improving outcome. Recently, Pomerantz and Dutton [33] applied PLG during endoscopic sinus surgery to improve their packing technique. Their quality-of-life scores showed an improvement in terms of postoperative epistaxis, synechia formation, and exuberant granulation tissue in PLG-treated patients.

Synthetic and allogeneic implants

Synthetic meshes and allogeneic implants are currently used in ‘‘tension-free’’ hernioplasty of the abdominal wall and in inguinal hernia repair [34]. However, after cicatricial hernia repair, serious complications have been observed (i.e., seromata, dense adhesions, fistulization). Furthermore, Tyrell et al. [35] observed that the tensile strength of implanted meshes was markedly reduced due to absorption of the mesh. Lichtenstein hernioplasty is an accepted method for inguinal hernia repair. One of the most frequent complications after inguinal hernia surgery is postoperative pain, which at times is chronic and permanent, leading to a poor quality of life [36, 37]. Innovative tools for decreasing the complication related to anchoring of the mesh in position include the use of tissue adhesives [38]. Another option for securing the synthetic implants may be realized by applying PLG to the meshes rather than to full suture lines. Autologous platelet growth factors have been used by Zieren et al. [39], who showed enhanced ingrowth and increased cell proliferation with a higher number of fibroblasts/collagen fibers in abdominal hernia repair, suggesting a role of platelet growth factors in the healing process. Sclafani et al. [40] showed an accelerated maturation of wounds

in an experimental setting when PLG was used. On the basis of these findings, we have initiated a research program to confirm whether the application of PLG is useful for hernia repair in a clinical setting. The study objective is to determine the advantages of PLG use as compared with current techniques, especially in minimizing pain after conventional and laparoscopic hernioplasties.

Bone growth

Impaired bone healing after fractures, with the development of pseudarthrosis, or fusion operations in the case of nonunions cause pain and disability. Attempts are being made to create bone substitutes, but technologies are being developed that improve bone healing by adding biologic materials, such as PLG, to stimulate osteogenesis and osteoconduction. In bone healing (i.e., callus formation), platelets act as an exogenous source of growth factors stimulating the activity of bone cells on the basis of a unique role in bone growth [41, 42].

Numerous *in vitro* studies using platelet gels have been performed. Since the initial description of PLG use in maxillofacial surgery, subsequent studies have focused on the effect from a variety of bone-derived cells including osteoblasts, osteoclasts, periodontal ligament cells, and mesenchymal cells. Gruber et al. [43] demonstrated that proliferation of bone-derived cells was augmented, in a dose-dependent manner, when PLG was used. They suggested that, aside from a mitogenic effect, PLG application at the time of surgery enhances bone healing capacity due to bone resorption and remodeling.

Another therapeutic application of PLG involves the combination of PLG with different bone substitutes. Several authors have used histomorphometric analysis to demonstrate a beneficial effect of PLG when different bone matrices are used. Aghaloo et al. [44] used natural deproteinized bovine matrix and measured improved bone growth when it was used with PLG. Suba et al. [45] used β-tricalcium phosphate in combination with PLG and observed more intense bone regeneration. Furthermore, due to the sticky structure of PLG, caused by the fibrin strands present in the gel, bone substitutes are kept together, avoiding unwanted migration of bone particles.

Recently, the percutaneous application of PLG in a diabetic femur fracture model was described. Normalized cellular proliferation and chondrogenesis, with improved mechanical strength, were observed when PLG was injected in this model [46].

Tissue engineering

A variety of methods have been used for the restoration of bone or soft tissue defects in different surgical settings, including orthopedic surgery, maxillofacial surgery, and reconstructive surgery [47, 48]. However, the manipulation and reinforcement of biocompatible materials in surgery is not always easy to achieve. Mixtures of autologous tissues have been used to accomplish restoration of defects. Tissue engineering, a technology involving the morphogenesis of new tissues using isolated cells with biocompatible matrices, often is combined with growth factors. Mesenchymal stem cells (MSC) are multipotent cells that can replicate as undifferentiated cells with the possibility of differentiating into mesenchymal tissues (i.e., bone, cartilage, tendon, muscle). This ability has made MSC a potential component of tissue engineering concepts. Recently, several research groups have been studying PLG as a matrix for tissue-engineering models because the activated PLG releases numerous platelet-derived growth factors [49, 50].

Another advantage of using MSC and PLG is that these two components are autologous, nontoxic, and biodegradable, proportional to the development of new bone formation, as compared with allogeneic matrices, which are nondegradable during the first weeks after implantation [51].

Yamada et al. [52] demonstrated in dogs that the combination of MSC and PLG resulted in a significantly higher maturation of bone and neovasularization than observed in control subjects. Thereafter, the same group used a combination of MSC and PLG for successful clinical alveolar bone augmentation [47]. The clinical application of PLG with bone marrow–derived MSC also was reported by Kito et al. [53] in the course of distraction osteogenesis. In soft tissue engineering, Anitua et al. [54] identified the role of PLG releasate on cultured tendon cells. These authors state that the treatment of tendon injuries may be of benefit because cell proliferation is induced with the promotion of endogenous angiogenic growth factor synthesis.

Infection prevention

Many investigators have focused on the exogenous application of concentrated and activated platelets in PLG for a variety of procedures that result in the material adhering to tissues, thereby initiating and accelerating wound healing [17, 22]. However, in addition to the platelet gel delivery of growth factors, limited data are available that address the role of leucocytes present in PLG to act as an antimicrobial component [10]. From our own experience, we have reported that P-LRP not only comprises a high concentration of platelets containing platelet growth factors, but that it also is abundant in concentrated leukocytes, neutrophils, monocytes, and lymphocytes [11]. Neutrophils and monocytes are rich in granules containing myeloperoxidase, which catalyzes the oxidation of chloride to generate hypochlorous acid and other reactive oxygen derivates that act as potent bactericidal oxidants toxic to microorganisms and fungi [55, 56].

Furthermore, Yeaman et al. [57] and Tang et al. [58] support the idea that platelets also are involved in microbicidal activity, suggesting that they play a role in the platelet host defense mechanism by releasing a variety of platelet microbicidal proteins. The platelet microbicidal proteins were shown to be released after platelet acti-

vation, demonstrating potent activities against pathogens that have a tendency to enter the bloodstream [59].

Furthermore, we expect that exogenous PLG injections rather than periarticular injections with corticosteroids or even surgery will be indicated for the treatment of tendonitis and periarthritis. Such a therapeutic approach was cautiously suggested in an equine study that applied PLG to injured tendons [60].

Conclusion

Platelet–leukocyte gels may become an ideal autologously prepared biologic blood-derived product that can be exogenously applied to a diversity of tissues, in which it releases high concentrations of platelet growth factors that enhance healing. In addition, it possesses antimicrobial properties that may contribute to the prevention of infections.

The current review suggests that the use of PLG may be beneficial in surgery. Platelet–leukocyte gels have been successfully used in maxillofacial surgery, orthopedics, cosmetic surgery, and dental implantology. However, the procedure for preparing PLG and the techniques of application are likely to differ greatly among clinicians, resulting in inconsistent results. To avoid conflicting data, standardization of P-LRP methodology is therefore warranted. Furthermore, randomized controlled clinical trials are needed to study the effect of PLG on wound rehabilitation, functional recovery, and the promotion of bone growth. The bactericidal effect of PLG should be clarified, and its role in tissue engineering should be defined. Overall, it may be concluded that the structures present in PLG appear to have a major beneficial therapeutic effect in surgery.

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