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Platelet-Rich Plasma in Burn Treatment

Mehmet Unal

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Abstract

As a general definition, platelet-rich plasma (PRP) is the concentration of autologous human platelets in a small amount of plasma. PRP contains important growth factors deposited in alpha-granules of platelets and plasma proteins such as fibrin, fibronectin, and vitronectin. PRP has been shown to improve wound healing process in acute trauma wounds, incisional wounds, and chronic nonhealing wounds and is a beneficial agent in reconstructions of soft and hard tissue. Furthermore, PRP enhances differentiation of epithelial cell and collagen bundle organization. Effects of growth factors in PRP on wound healing and successful results obtained with PRP treatment in other types of wound lead to the use of PRP for burn treatment.

Keywords: burn injury, wound, healing, platelet, platelet-rich plasma

1. Introduction

Platelets are small and anucleate cells derived from megakaryocytes in the bone marrow. Platelets carry vesicles containing presynthesized proteins in their granules that can be released into the local environment or transported for surface expression. Controlled and coordinated release of these factors is an important part of the normal wound healing process.

Platelet-rich plasma (PRP) is a composition comprising platelets in a plasma at a higher density than normal blood concentration. PRP has been shown to be an effective agent for bone grafting, cartilage regeneration, neovascularization, and tissue deposition in animal studies. These results have increased the interest in PRP and led to the use of PRP in human surgical applications.

PRP has been reported to be used in a wide variety of applications, mainly in problematic wound, maxillofacial, and spinal surgery. The results from these studies have provided strong evidence supporting the clinical use of PRP; however, only few include controls to clearly demonstrate the role of the PRP. Additionally, there is not a precise consensus regarding

platelet-rich plasma production and characterization. This lack of consensus also prevents a standard approach in the PRP [1–9].

2. Platelets: origin, structure, distribution, and their roles in hemostasis

Platelets, discovered in the nineteenth century, are small, nucleus-free cytoplasmic cellular structures which are round or oval-shaped and have about 2 μm diameter and derived from megakaryocytes (a type of white blood cell) in the bone marrow [1]. These cellular structures were initially believed to be involved only in the hemostasis and pathological thrombus formation. Although, platelets do not have nucleus, many organelles are found in their cytoplasm including abundant mitochondria, several loops of microtubular coils giving them a robust cytoskeletal structure, and granules (alpha, delta, and lambda) [2–5].

The platelets organize the migration of cells associated with wound healing (neutrophils, macrophages, stem cells, etc.) as well as the formation of the initial clot by means of the inflammatory mediators they contain [6, 7].

Alpha granules are formed during megakaryocyte maturation, and each platelet contains approximately 50–80 alpha granules, each bound by a unit membrane [8, 9]. Alpha granules are about 200–500 nm in diameter and contain more than 30 bioactive mediators each playing a fundamental role in hemostasis and/or tissue healing. Platelets reside intravascularly and are concentrated in the spleen. The normal mean concentration of platelets in normal blood is about 140,000–400,000 platelets/mm^3. Platelets are removed by macrophages in the reticuloendothelial system after approximately 10 days in the circulation [9–11].

After tissue damage, the platelets become exposed to the damaged vessel, and these damaged vessels are places where the platelets directly contact with collagen, the basement membranes of capillaries, and subendothelial microfibrils [10]. This interaction causes the platelets to aggregate at the damaged site and change from a rounded shape to one that includes large, sticky protuberances or pseudopodia. This course is called "activation." The alpha-granules fuse with the platelet plasma membrane and release their protein contents to the surroundings during activation [11, 12].

Blood clotting begins via one of two pathways called intrinsic and extrinsic pathways [10]. The intrinsic one is started by damage or alteration to the blood, itself, whereas the extrinsic pathway is started via the contact of blood and factors that are extraneous to the blood (e.g., damaged tissue). Both cascades are associated with a series of reactions in which the inactive factors are activated. These series of reactions facilitate the formation of other mediators from precursors that go on to catalyze subsequent reactions, leading to the formation of a final clot. Although both pathways are initiated in different ways, they overlap and share common steps in the later stages of clot formation [9, 11]. The platelets participate in many levels of the reaction sequence that produces fibrin thread and are component of the final clot structure, which comprise a fibrin mesh, with the activated platelet aggregate and red and white blood cell complex within. Since calcium ions are necessary for blood clotting, an effective agent capable of binding calcium ions or removing it from the environment prevents the progress of the coagulation process. Citrate, which binds to calcium ions and forms the calcium citrate

molecule, is a soluble but unionizable substance. Classical blood preservatives include citrate dextrose and citrate phosphate dextrose as well as other substances to maintain cellular viability [9, 13–15].

3. Wound healing process

There are three overlapping stages to wound healing: inflammatory, proliferative, and remodeling. Inflammation is the first response to tissue damage. The goal is to provide rapid hemostasis and initiate a series of reactions leading to tissue regeneration. When blood exits from damaged vessels, a hematoma that fills the tissue space occurs, and platelets have crucial roles in this process. Cytokines and growth factors released from activated platelets and other cells result in several events, including cell migration, proliferation, differentiation, and matrix synthesis [16–19]. The fibrin mesh in the hematoma serves as a transient matrix to continue regenerative space and ensure a scaffold for migration and proliferation of cells [18, 20].

Neutrophils, inflammatory cells which first infiltrate the wound area and have lifetimes limited to hours and days, provide rapid defense against infections and removal of tissue debris. Then a flow of monocytes and T lymphocytes occurs to wound area [16, 17, 19, 21].

After monocytes reach the wound area, they differentiate into macrophages, and macrophages become predominant cell types in this region. The macrophages, which have lifetimes limited to days to months, support neutrophils in their functions and increase secretion of factors from neutrophils [16–18, 21]. The role of T lymphocytes in a successful wound healing process is still not clearly understood [19]. The mesenchymal stem cells migrate to the wound site to form an unstable cell line that will serve as a skeleton for or formation of the bone, cartilage, fibrous tissue, blood vessels, and other tissues [17]. Fibroblasts migrate to the wound site and begin to proliferate to produce extracellular matrix [17, 22]. Blood vessel endothelium close to the injury area proliferates to create new capillaries, and then these new vessels extend to the damaged site. These activities are regarded as the first steps of angiogenesis [16, 17].

During the proliferative phase, which is the second stage of wound healing, damaged and necrotic tissue is removed from the surrounding and replaced by living tissue that is in accordance with the original tissue structure of that region (e.g., bone, cartilage, fibrous tissue). Mesenchymal stem cells differentiate into fibroblasts, osteoblasts, chondrocytes, and other cell types which are required to produce the appropriate tissue type [17].

The third phase, the remodeling phase, is the final stage of wound healing. During this phase, the newly generated tissue reshapes and reorganizes to more closely resemble the original tissue [17].

4. Roles of platelets in wound healing

A lot of proteins are found within the alpha granules of platelets that strongly influence wound healing process, including transforming growth factor (TGF)-beta, platelet-derived growth factor (PDGF), platelet-derived endothelial growth factor (PDEGF), platelet-derived angiogenesis

Growth factor	Function in wound healing
Connective tissue growth factor (CTGF)	• Proliferation, migration, and tube formation of vascular endothelial cells and angiogenesis • Proliferation and differentiation of osteoblasts and matrix mineralization
aFGF or FGF-1 (fibroblast growth factor; acidic)	• Promotes skin-derived keratinocytes, dermal fibroblasts, and vascular endothelial cells • Participates in proliferation, differentiation, angiogenesis, and cell migration
bFGF or FGF-2 (fibroblast growth factor; basic)	• Promotes angiogenesis, endothelial cell proliferation, collagen synthesis, matrix synthesis, and epithelization • Growth of fibroblasts, myoblasts, osteoblasts, neural cells, endothelial cells, keratinocytes, and chondrocytes
GM-CDF or CSF a (granulocyte/macrophage colony-stimulating factor)	• Chemoattractant for neutrophils • Participates in the proliferation and differentiation of osteoblasts and in the proliferation of BM progenitor cells
Insulin-like growth factor (IGF)	• Growth factors for normal fibroblasts, promotes the synthesis of collagenase and prostaglandin E2 in fibroblasts • Induces collagen and matrix synthesis by bone cells, regulating the metabolism of joint cartilage
Interleukin-1b (IL-1b)	• Activates osteoclasts in high concentrations and suppresses the formation of the new bone. In low concentrations, however, promotes new bone growth • Enhances inflammatory reactions and collagenase activity and inhibits the growth of endothelial cells and hepatocytes
Interleukin-8 (IL-8)	• Stimulates mitosis of epidermal cells and supports angiogenesis
Keratinocyte growth factor (KGF or FGF-7)	• Most potent GF for skin keratinocytes • Promotes wound healing via proliferation, differentiation, angiogenesis, and cell migration • Stimulates mitosis of epithelial cells except for fibroblasts and endothelial cells
Platelet-derived growth factor (PDGF)	• Activates TGF-b and stimulates neutrophils, macrophages, and mitosis of fibroblasts and smooth muscle cells, collagen synthesis, collagenase activity, and angiogenesis • Chemoattractant for hematopoietic and mesenchymal cells, fibroblasts, and muscle cells. Stimulates chemotaxis toward a gradient of PDGF
Transforming growth factor alpha (TGF-a)	• Affects bone formation and remodeling by inhibition of synthesis of collagen and release of calcium • More potent than EGF • Promotes the generation of osteoblasts and deposition of bone matrix during osteogenesis • Stimulates mesenchymal, epithelial, and endothelial cell growth. Endothelial chemotaxis controls the epidermal development
Transforming growth factor beta (TGF-b1)	• Fibroblast chemotaxis, proliferation, and stimulates collagen synthesis • Growth inhibitor for epithelial and endothelial cells, fibroblasts, neuronal cells, hematopoietic cell types, and keratinocyte
Tumor necrosis factor alpha (TNFa)	• Growth factor for fibroblasts and promotes angiogenesis
Vascular endothelial growth factor (VEGF/VEP)	• Induces neovascularization by stimulating the proliferation of macrovascular endothelial cells • Stimulates the synthesis of metalloproteinase that helps degrade interstitial collagen types 1, 2, and 3

Table 1. Growth factors in platelet and their function.

factor (PDAF), platelet factor 4 (PF4), vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), epithelial cell growth factor (ECGF), insulin-like growth factor (IGF), interleukin (IL)-1, osteocalcin, osteonectin, vitronectin, fibrinogen, fibronectin, and thrombospondin (TSP)-1 [8, 11, 13, 16, 20, 21, 23, 24]. Collectively, these proteins mentioned are members of the growth factor, cytokine, and chemokine families. Each of these proteins takes a position in different steps of wound healing (**Table 1**) [9, 21]. Platelets begin to actively secrete these mediators within 10 minutes after clotting, and more than 95% of these presynthesized growth factors are secreted within 1 h [9, 21].

5. Platelet-rich plasma (PRP)

As a general definition, PRP is the concentration of autologous human platelets in a small amount of plasma. There are many different names, types, and PRP-like products (**Table 2**) [2–28]. PRP was first described by Marx et al. [2–28].

Some investigators have suggested that the platelet concentration in PRP should be at least 3–5 times the normal platelet concentration in the blood (**Table 3**) [29–32], although the dependence of clinical benefit on platelet concentration versus total number of platelets delivered may need to await further investigation [33]. Platelet concentration ratios of less than twofold to 8.5-fold have been reported [21, 29–31, 34–36]. Weibrich et al. [24] recommend that different individuals may need different platelet concentration ratios to obtain comparable biological effect.

PRP comprises not only high levels of platelets but also all components of clotting factors. For PRP to be clinically effective, it is emphasized that each 1 microliter of PRP should have at least 1,000,000 thrombocytes. (**Tables 3** and **4**) [29–32, 37].

Platelet-rich plasma (PRP)	Nonactivated plasma with amount of platelets above baseline
Platelet-rich fibrin (PRF)	Platelet-rich product with 3D structure
Platelet concentrate	Platelet-rich plasma
Plasma rich in growth factors	Type of pure PRP, no leukocytes
Platelet gel	Activated PRP
Platelet lysate	Activated PRP by lyses, e.g., by freeze-thawing or Triton-X
Platelet releasate	Activated PRP by thrombin and calcium chloride

Table 2. An overview of different names, types, and PRP-like products.

Thrombocytes baseline whole blood ($\times 10^9$/L)	519.6 ± 214.3
Thrombocytes PRP ($\times 10^9$/L)	2139.3 ± 1401.6
Ratio thrombocytes PRP/baseline whole blood	3.9 ± 1.8

Table 3. Platelets of the whole blood and PRP.

Growth factor	Physiologic level in the blood	Level in PRP
PDGF-β	3.3 ± 0.9 ng/ml	17 ± 8 ng/ml
TGF-β1	35 ± 8 ng/ml	120 ± 42 ng/ml
VEGF	155 ± 110 pg/ml	955 ± 1030 pg/ml
EGF	129 ± 61 pg/ml	470 ± 320 pg/ml

Table 4. Levels of some growth factors in blood versus PRP.

PRP acts through the degradation of alpha granules in the platelets. Secretion of growth factors begins from alpha granules within 10 min after clotting and more than 95% of the presynthesized growth factors secreted within 1 hour. In practice, after the PRP is prepared, it is necessary to induce the alpha granules in platelets for the release of growth factors. This induction is made by adding calcium and/or thrombin into PRP prepared in vitro. For this reason, the PRP should be prepared without clotting and should be applied within 10 minutes after clot initiation [9]. Basically, PRP is acquired by centrifuging autologous blood at a certain cycle. To keep the integrity of platelet membrane, acid citrate dextrose type A is used as anticoagulant agent [38].

While preparing the PRP, common points in clinical preparation techniques are like that: The blood is collected from the patient and is taken into the tube containing anticoagulant agent, and immediately centrifuge operation is initiated. When blood containing anticoagulant agent is centrifuged, three layers form as a result of the density: the deep layer containing red blood cells (gravity, 1.09), the middle layer containing white blood cells and platelets (buffy coat; gravity, 1.06), and the top layer (platelet poor plasma; gravity, 1.03) [11].

In the second stage, different techniques are applied, but basically, acellular plasma layer and the red cell layer are removed, and only "buffy coat" layer which contains dense platelet and white blood cells is obtained. So, the PRP becomes ready to be applied after addition of calcium and/or thrombin to activate thrombocytes [9].

Additionally, approximately 6 ml of platelet-rich plasma can be produced from 45 to 60 ml of blood thanks to newly developed small, compact office systems [14, 21, 39–41]. Numerous of such systems are available in use, including the PCCS (Implant Innovations, Inc., Palm Beach Gardens, Fla.), the Symphony II (DePuy, Warsaw, Ind.), the GPS (Biomet, Warsaw, Ind.), the Magellan (Medtronic, Minneapolis, Minn.), and the SmartPReP (Harvest Technologies Corp., Norwell, Mass.). Though, all these systems work on a small volume of obtained blood (45–60 ml) and on the principle of centrifugation, they have many differences in their capacity to collect and concentrate platelets, with about 30–85% of the available platelets collected and from a less than twofold to an approximately eightfold rise in the concentration of platelets over baseline [15, 30, 33, 35, 40, 42].

Although it is possible to produce PRP by using standard laboratory centrifuge, this process needs much effort, usually requiring multiple transfers and two spins; therefore, it may be difficult to maintain the sterility [14, 31, 43]. Moreover, these techniques may not be reliable to maximize platelet concentration or the levels of key secretory proteins [21].

PRP is stable, in the anticoagulated state, for up to 8 h after preparation. This duration allows to be used even during long operations [14, 21, 44]. In order to release the contents of alpha

granules in the platelets, PRP must be activated. For this purpose, most commonly, 1000 units of topical bovine thrombin per milliliter of 10% calcium chloride solution is added to the platelet-rich plasma [16, 34, 39, 45].

6. PRP in wound healing

There are studies evaluating the effects of PRP on wound healing (**Table 5**) [37, 46, 47]. In the early phase of wound healing, the clot formed in the injury area serves as a matrix for cell migration, and this phase is primarily effected by platelets. Platelets contain over 1100 proteins, including growth factors, immune system mediators, enzymes, enzyme inhibitors, and bioactive compounds involved in the wound healing process. PRP contains important growth

Name	Type of wound	Method of use	Results
Almdahl et al.	Saphenous vein harvest site	PRP was sprayed on the wound before closure	No difference for the infection rate and cosmetic scale
Bahar et al.	Acute pilonidal abscess surgical site	The cavity was completely filled with PRP 24/36 h after surgery and covered with Vaseline gas	No healing time difference Significant difference for the test group on a pain relief scale and regarding the time to return to work
Kazakos et al.	Acute limb soft tissue wounds	Application of PRP gel once weekly	Significant difference for the test group regarding the time before reconstructive surgery by skin graft
Lawlor et al.	Surgical incisions for vascular surgery	PRP is sprayed during wound closure	No difference for the infection rate
Spyridakis et al.	Surgical excision of pilonidal sinus left opened for secondary healing	Application on the wound of PG on postoperative days 4 and 12	Significant difference for the test group regarding the complete healing time and quality of life
Han et al.	Full-thickness 5 mm punch wounds	Application on the wound	Significant difference for the test group regarding epithelialization at the tenth day
Hom et al.	Full-thickness 4 mm punch wounds	Application on the wound bed on postoperative days 0 and 7	Significant difference for test group regarding the healing time
Lee et al.	Full-thickness 2.5 × 2.5 cm skin wounds	Application on the wound	No difference regarding the healing rate
Molina-Minafio et al.	Full-thickness 6 mm punch wounds	Application on the wound	Significant difference for the test group regarding epithelialization at day 7 but not at day 28
Khalafi et al.	Sternal closure and saphenous vein harvest site	Application of PRP on the sternum, on the subcutaneous tissue, and on the wound edges	Significant difference for the test group regarding chest infection No difference regarding the saphenous vein harvest site infection rate Significant difference for the test group regarding chest and leg excessive drainage

Table 5. Some studies using PRP for wound healing.

factors deposited in alpha granules of platelets and plasma proteins such as fibrin, fibronectin, and vitronectin [37, 46, 47]. While plasma proteins serve as a skeleton for the bone, connective tissue, and epithelial migration, cocktail of growth factors plays an important role in tissue repair and regeneration. Degradation of previously stored growth factors occurs after contact with coagulation triggers such as collagen and tissue thromboplastin. Platelet activation with exogenous thrombin is associated with massive thrombin release and may reduce biological activity. Ten minutes after platelet activation, platelets start to deliver growth factors and give 95% of these molecules to environment in an hour [21]. Therefore, platelets should be applied within 10 min after activation. After release growth factors attach to mesenchymal stem cells, osteoblasts, fibroblasts, endothelial cells, and transmembrane receptors expressed by epidermal cells. The best known growth factors are platelet-derived growth factor, fibroblast growth factor, transforming growth factor beta, epidermal growth factor, vascular endothelial growth factor, and insulin-like growth factor. This attachment triggers the internal signaling pathway and leads to the expression of gene sequences that increase the normal wound healing process, such as cell proliferation, matrix formation, osteoid production, and collagen synthesis. Topical application of PRP accelerates the reepithelialization process by upregulating regulatory proteins of cell cycle such as cyclin A and CDK4. PRP is a potent matrix metalloproteinase (MMP)-1 stimulator and, thus, allows the extracellular matrix to be reorganized during wound healing [48, 49].

PRP may also suppress inflammation by suppressing cytokine release and increases regeneration and reepithelization by triggering capillary angiogenesis. The involvement of macrophages in the wound healing process is also mediated by signal proteins released from platelets. PRP has also been reported to exhibit antimicrobial activity against microorganisms such as *Escherichia coli*, MRSA, *Candida albicans*, and *Cryptococcus neoformans* and to have analgesic effect. Additionally, the pH 6.5–6.7 of the PRP may explain its antibacterial property. Although it has been suggested that leukocytes in PRP accelerate the recovery of soft tissue injury by suppressing bacterial growth, it has been also claimed that PRP may cause local pain and even suppress the healing process due to the inflammatory cytokines in it [50, 51].

In order for PRP therapy to be effective, it should contain 3–5 times the normal platelet level (approximately $0.8–1 \times 10^6/\mu L$). It is thought that, at very high platelet concentrations, it can suppress the wound healing with an opposite effect, because increase of the bioactive substances does not always mean a better effect. For example, at platelet concentrations higher than $1.5 \times 10^6/\mu L$, angiogenesis is suppressed. Eppley emphasizes that it is very difficult to achieve the desired platelet concentration because of the large number of variable and potential interactions [24, 35, 52].

A relation between growth factors in PRP with age and gender has not been detected. Since factors in PRP do not enter the cell or into the nucleus, it is assumed that there are no mitogenic or carcinogenic properties of PRP [46].

The use of PRP is contraindicated in coagulation defects (thrombocytopenia, anticoagulant use, hypofibrinogenemia), anemic situations, hemodynamic instability, and bovine thrombin hypersensitivity [53, 54].

7. PRP in burns

Growth factors play a crucial role in normal wound healing as well as impaired wound healing. Growth factors, such as insulin-like growth factor-1 (IGF-1) and platelet-derived endothelial cell growth factor (PDGF), inhibit apoptosis pathways which provide a rapid cell turnover and, thus, catalyze the physiologic wound healing in different steps. It is also thought that direct or indirect effects of growth hormone on wound healing are related to IGF-1 expression [55].

PRP is a new therapeutic option that is increasingly used especially in the treatment of soft and bony tissue defects to increase the tissue formation capacity and in improvement of chronic wound healing process [56–59]. Platelet-rich plasma, a rich source of growth factors released by activated platelets, is obtained from centrifuged blood which is combined with calcium chloride and thrombin [57, 58, 60].

Platelets are critical in the wound healing process and migrate to the wound site immediately and initiate coagulation when any damage occurs. Platelets are good sources of growth factors and cytokines associated with wound healing. Multiple growth factors and cytokines, including platelet-derived endothelial cell growth factor (PDGF), transforming growth factor-b (TGF-b1 and TGF-b2), transforming growth factor-a (TGF-a), platelet thromboplastin, thrombospondin, platelet-activating growth factor-4, vascular endothelial growth factor (VEGF), epidermal growth factor (EGF), coagulation factors, fibroblast growth factor (FGF), calcium, serotonin, histamine, and hydrolytic enzymes, with degranulation triggered by proteins such as thrombin are released by platelets [57, 58, 60].

Growth factors are key components of cellular activities related to wound repair. Growth factors mediate the migration of inflammatory cells into the wound site; they induce cell proliferation and differentiation and enhance extracellular matrix production and accumulation. Transforming growth factor beta is known to be an important mediator in tissue repair and has proven to be therapeutic in chronic nonhealing wounds [61, 62]. Platelet-derived endothelial cell growth factor promotes dermal regeneration, provokes protein and collagen synthesis that provides migration and angiogenesis, and increases TGF beta expression. Both transforming growth factor beta and platelet-derived endothelial cell growth factor are found at higher densities in PRP than platelet-poor plasma (PPP) [61].

Burn injury is a major reason of trauma that can result in death or disability, which requires a long recovery duration and high health care costs. In burn trauma, depth and size of burn injury, burn area, and patient age are the most important factors that affect the morbidity and mortality. Burn depth is also the most important parameter that determines the long-term appearance and functionality of the patient [63]. Conditions such as immunosuppression, extensive burn area, and malnutrition ensure an appropriate milieu for microorganisms, and unfortunately, infections are common and among the most important causes of morbidity and mortality in burn patients. Although the mortality rate is reduced with new treatment approaches in burn injuries, secondary infections and long recovery duration can still cause mortality. Early debridement and skin grafts can yield successful results, but inadequate graft

donor area and unsuitable patient circumstances for surgery of burn patients are important obstacles for skin grafting [55, 62].

In these cases, using products that accelerate the wound healing process affects the morbidity and mortality of patients. Many different kinds of dressings or pharmacotherapies have been developed for this purpose, but these are very expensive, and mechanisms of action of these therapies are not fully documented [64–66]. Unfortunately, no optimal wound cover materials are currently available, but desired features of these materials include supporting increasing cells in wound healing, allowing vessel proliferation, keratinocyte adhesion, and differentiation and forming a barrier against fluid loss and microorganisms [62].

Platelet-rich plasma includes platelets, growth factors, cytokines, and clotting factors in high levels. Platelets in PRP initiate releasing these activated mediators in 10 min after clotting, and in the first hour, more than 95% of growth factors are released. Platelet-rich plasma stays stable, without losing its effectiveness, for approximately 8 h after preparation [57, 58]. PRP contain many different mediators, but TGF-b and PDGF are thought as the most important growth factors in PRP. They are involved in many stages of wound healing by triggering cell development and differentiation. Previous in vivo and in vitro studies have shown that cells which have roles in wound healing process are susceptible to growth factors [59]. Fibroblastatin is known to be sensitive to PDGFa, PDGFb, IGF, bFGF, and EGF [67]. Epidermal growth factor acts as a chemotactic factor for fibroblasts and, also, when administered topically enhances epidermal regeneration and strength of wound tension [59]. Endothelial cells are susceptible to VEGF and bFGF [68]. Growth factors such as VEGF, PDGF, and bFGF are triggers for vessel proliferation [69]. Fibroblast and smooth muscle cell migration and proliferation are induced by platelet-derived endothelial cell growth factor; also it is shown that PDGF is a chemotactic factor for neutrophils and monocytes and increases collagen deposition [60]. Additionally, PDGF and bFGF promote chondrocyte, osteoblast, and periosteal cell proliferation [70]. Transforming growth factor-b1 acts as a regulator for cell differentiation, proliferation, chemotaxis, and synthesis of some extracellular matrix proteins [60]. The effects of enhancing collagen synthesis, granulation tissue, and strength of wound tension of TGF-b1 were observed in animal studies [59, 71]. Another effect of TGF-b is the promotion of suprabasal cell proliferation and epidermal regeneration. Furthermore, TGF-b stimulates glycosaminoglycan, collagen, and fibronectin synthesis from fibroblasts. Transforming growth factor-b induces collagen synthesis and accelerates collagen maturation in the early period of wound healing. In addition, it is shown that using TGF-b with PDGF increases collagen deposition effects of TGF-b [60].

PRP has been shown to improve wound healing process in acute trauma wounds, incisional wounds, and chronic nonhealing wounds and is a beneficial agent in reconstructions of soft and hard tissues. Furthermore, PRP enhances differentiation of epithelial cell and collagen bundle organization. In PRP-treated wounds, the inflammatory phase of wound healing is shortened, and prolonged inflammation process is not seen. These effects of PRP reduce bacterial infections and scar formation [56, 57, 59, 60, 62, 71].

Effects of growth factors in PRP on wound healing and successful results obtained with PRP treatment in other types of wound lead to the use of PRP for burn treatment. Despite the paucity of the literature on PRP in burns (**Table 6**) [72], in theory, a dermal burn could benefit from PRP in several ways. First, hemostatic qualities of PRP could reduce perioperative blood

Name	Type of wound	Method of use	Results
Klosova et al.	Split-thickness skin graft on deep burns	Application of PG on the skin graft	PG accelerates reaching normal elasticity for split-thickness skin graft (no statistical analysis)
Maciel et al.	Burn with an iron	Application of PG on the wound and 3 days later	PG accelerates complete healing (no statistical analysis)
Henderson et al.	Ultrapulse CO_2 laser 232 cm burns	Application of PG	No difference regarding reepithelialization

Table 6. PRP in burns.

loss, as well as improve the take rate of the skin grafts by decreasing continued bleeding, functioning as a fibrin glue, as well as providing a well-vascularized bed for the meshed skin graft. Furthermore, the positive effects of PRP on wound healing, as seen in reports on PRP in in vitro models, chronic and acute wounds, could contribute to faster closure of mesh interstices, because PRP promotes vascular ingrowth and fibroblast proliferation and possibly reepithelialization. A deep dermal burn also could benefit from PRP through its hemostatic antimicrobial abilities [73–76].

The addition of PRP to the graft site has been shown to accelerate wound healing and enhance epithelialization and angiogenesis in split-thickness skin grafts and donor sites. Klosová et al. reported that combination of split-thickness skin grafting (STSG) and autologous platelet concentrate reversed the viscoelastic properties of scars to the plateau state more rapidly than areas treated with STSG alone [77–79].

In a recent study, it was demonstrated that PRP provided a quick repair of the extracellular matrix and its components in deep second-degree burn wounds in horses, and also, it was observed that two applications of PRP treatment accelerated formation of extracellular matrix during the first half of wound healing [80]. Additionally, Hao et al. reported that using PRP with acellular xenogeneic dermal matrix for treatment of deep second-degree burns decreased infection rate and increased wound healing [62, 81].

On the other hand, it is ambiguous whether results obtained in chronic and acute wounds could be applicable in burn injury wounds because a burn wound has a distinct physiological features than these wounds, including an enhanced inflammatory response, both systemic and local; increased edema; and a reduced perfusion secondary to hypercoagulability and microthrombus formation [82–84]. Patients affected by burn trauma are in a changed systemic physiological status [82, 84] when compared with the other healthy subjects in whom PRP mostly has been used and studied so far. It is generally recommended to withdraw blood before surgery to avoid activation of the platelets, but apparently this is not possible in burn patients, in whom platelets are already massively activated. It is known that platelets of burn patients show a distinct course in time, with a nadir at postburn day 3 followed by a reactive peak at postburn day 15, with a gradual return to normal values around postburn day. Several factors such as burn surface area, age, and sepsis influence this time course. There is little data about how burns or other traumas affect platelet and platelet function. In patients who have been exposed to trauma, it has been demonstrated that platelets were activated at least 72 h after injury and had an increased functionality in the first 48 h. This might affect the quality of PRP and the timing of its application in burn patients [76].

The long term effect of PRP on scar formation after burn injury is another important consideration and has not yet been evaluated comprehensively. There are plenty of growth factors released from the platelets and leukocytes in PRP, and some of these growth factors are chemotactic in recruiting inflammatory cells and a prolonged inflammation which could cause hypertrophic scar [85]. Furthermore, scar formation consists of series of complex events, and the effects of single growth factors in this process are still being unraveled. Among the growth factors, TGF-β1, TGF-β2, and platelet-derived growth factor are especially remarkable, because these factors are associated with hypertrophic and keloid scarring of normal skin wounds as well as in burn wounds. On the other hand, how PRP, a cocktail of many different growth factors, might influence scar formation remains to be seen. There are a limited number of publications on the development of hypertrophic scarring after the use of PRP in wound healing until now, and most of these publications are not related to burn trauma [76]. One of these studies is authored by Prochazka et al. They reported that while in burn patients treated with PRP combination, the rate of reepithelialization may not have been higher or faster than traditionally observed, the inflammatory markers normalized faster, providing the reepithelialized wound more stable. Because patients treated with PRP combination showed minimal cicatrization, they had high quality of healing without evidence of scar hypertrophy or contractures [76]. Additionally, recently some reports were published with positive results of PRP in combination with adipose cells for scar treatment; therefore, there might be an indication for PRP in the reconstructive aspect of burn treatment. On the other hand, in another study, long-term follow-up results did not show significant differences in scar quality in patients treated with PRP combination [86].

Furthermore, PRP treatment provides less pain and pruritus during the wound healing in burn trauma. And, one of the most important benefits of PRP in burn therapy is the cost-effectiveness of the therapy. The cost of hospital stay is lower (approximately 25% less) than that of patients who did not receive PRP combination treatment [87, 88].

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