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Wound healing is a complex process mediated by interacting molecular signals involving mediators and cellular events. It is followed by mesenchymal cell recruitment, proliferation, and extracellular matrix generation, which allows for scar formation. These events are mediated and modulated by interacting molecular signals, primarily cytokines, and growth factors (GFs) that stimulate and modulate the main cellular activities that underscore the healing process.1,2 Several studies have demonstrated that chronic wounds may, in some cases, lack GFs due to decreased production, decreased release, trapping, excess degeneration, or an association of these mechanisms.3,4

Autologous platelets have been shown to promote tissue repair in several clinical situations as a source of healing factors. To regenerate an injured tissue, it is necessary to understand the participation of individual cell types and the role of soluble factors that contribute to the extrinsic and intrinsic healing properties of tissue. It is reported that several GFs play a key role in initiating and sustaining the different phases of tissue repair.
Platelet alpha-granules are rich in GFs such as platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), or vascular endothelial growth factor (VEGF). These factors play an important role in all phases of healing of the tissue by recruiting mesenchymal cells and also during the synthesis of the extracellular matrix. The topical application of platelet gel or platelet-rich plasma (PRP) provides exogenous GFs in situ. Therefore, PRP is a tool that contributes toward the release of GFs to the wound area, which in turn makes it useful in promoting the functional recovery of physiological tissue repair.

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### Key Points
- The objective of this study was to review published reports on the role of growth factors (GFs) in tissue regeneration, focusing on platelet-rich plasma (PRP), a natural source of GFs.
- A search of studies published between 2001 and 2012 reporting on the usefulness of GFs and PRP for the treatment of different wounds, using the MEDLINE, EMBASE, and Cochrane Library databases with the key words tissue regeneration, wound healing, growth factor, and platelet-rich plasma, was conducted.

### Method
A search of studies published between 2001 and 2012 reporting on the usefulness of GFs and PRP for the treatment of different wounds, using the MEDLINE, EMBASE, and Cochrane Library databases with the key words tissue regeneration, wound healing, growth factor, and platelet-rich plasma, was conducted. Titles and abstracts identified by the literature searches were read and reviewed. Those not appearing to meet key words were excluded and the others were reviewed in full.

### Growth Factors
Growth factors are polypeptides produced by the tissue on which they act. They regulate differentiation, proliferation, migration, and metabolism in target cells, regulating the synthesis of specific adhesion molecules that control cell-cell and cell-substrate interactions. Each GF can have either one or several essential functions for a specific cell, depending on the particular circumstances of the cell environment. Certain GFs, sometimes secreted by the cell, interact with other cells through their corresponding receptor, which transmits a signal to the cells stimulating them to produce proteins in the medium.

The most widely studied GFs in relation to tissue proliferation and repair include: bone morphogenetic proteins (BMPs) (eg, BMP-1, BMP-2, and BMP-3); PDGF; insulin-like growth factor (IGFs) (eg, IGF-1 and IGF-II); TGFs, especially TGF-β; fibroblast growth factors (FGFs) (ie, acid-FGF and basic-FGF); granulocyte macrophage colony stimulating factor; epidermal growth factor; and VEGF. An important role in repair processes, specifically in the inflammation stages, is also played by cytokines produced by white blood cells, including the interleukins (ILs) IL-1, IL-3, IL-6, and IL-8. All of these GFs and cytokines act to a greater or lesser extent during the different stages of wound healing (ie, tissue necrosis resolution, cell regeneration, cell proliferation and migration, extracellular matrix synthesis, epithelization, and remodeling).

Table 1 summarizes the functions of the main GFs in relation to different healing processes.

### Platelet-Rich Plasma
Platelets play an important role in the regenerative process of a wound by releasing an important number of mitogenic and inflammatory substances; hence, they represent a natural source of GFs. They contain 3 large storage compartments: alpha granules, dense granules, and lysosomes. All of these secretory granules contain GFs, proteins for coagulation, cell adhesion molecules, activation molecules, cytokines, integrins, and inflammatory molecules, among others, with most of these molecules being localized in alpha granules.

When a wound is made, platelets initiate the hemostatic process by creating a complex network to plug vessels. At this point, platelets change their structure from a soft circular shape to a spherical shape and develop pseudopodia. This promotes their aggregation and adherence by redistributing receptors for their subsequent activation and degranulation, which ruptures their molecule-loaded granules and releases GFs into the medium to regulate the repair of damaged tissues. Peripheral blood can be centrifuged to obtain PRP, a fraction of plasma with a high concentration of platelets (5-fold higher than baseline) and hence with a high concentration of biomolecules with regenerative potential. Although PRP and plasma rich in GFs are used interchangeably by clinicians, they are different concepts. The PRGF is the fraction obtained from PRP by activation with calcium chloride.

Platelet-rich plasma is used for tissue regeneration in different clinical settings and offers several advantages...
since it is neither toxic nor immunoreactive and can be readily obtained, inexpensively, from the blood of the patients themselves. Various studies have been published on the preparation and utilization of PRP for wound-healing, with controversial results. Marx et al reported the combination of PRP with a mixture containing 10% calcium chloride and bovine thrombin favored jaw reconstruction. The utilization of PRP has yielded satisfactory outcomes in dentistry and maxillofacial surgery, plastic surgery, trauma and orthopedics, ocular surgery, gastroenterology, and skin ulcers.

**Clinical Applications**

The clinical utilization of PRP is highly varied, and new applications are constantly being reported for conditions in which more effective or rapid healing is required.

**Dentistry.** Periodontal surgery and dentistry are probably the fields in which most research has been conducted and which have obtained the most positive outcomes related to PRP. Autologous platelet gel was first used in oral and maxillofacial surgery in a patient by Whitman et al as a co-adjuvant in the insertion of titanium implants. These authors concluded that the application of autologous platelet gel provided consolidation of the bone fragments and increased adherence of mucogingival flap. Numerous animal studies have demonstrated the benefits of using GFs and autologous plasma in oral cavity tissue regeneration.

The application of PRP after tooth extraction has proven beneficial for preventing alveolar osteitis and improving hemostasis as described by Mancuso et al in a clinical study with 117 patients treated with PRGF after oral surgery. The results showed that the rate of alveolar osteitis was lower (3.4%) in bony sites treated with PRGF than sites not treated with PRGF (12.8%). The PRGF-treated sites also showed better hemostasis at the time of discharge and objectively faster soft tissue flap healing. Its use when treating post-extraction bone defects resulted in greater buccolingual and buccopalatal bone width, higher bone density, and greater tissue coverage in comparison to non-PRP-treated defects. In another case report, the authors treated intrabone defects by adding PRP to a bone allograft in guided tissue regeneration and reported significant improvements in clinical insertion and bone filling.

**Keypoints**

- Platelets play an important role in the regenerative process of a wound by releasing an important number of mitogenic and inflammatory substances; hence, they represent a natural source of growth factors.
- Among the clinical applications of platelet-rich plasma are dentistry, plastic surgery, trauma and orthopedics, ocular surgery, gastroenterology, and skin ulcers.
simple and safe therapeutic approach in oral and maxillofacial surgery.35-38

In an in vitro study, García-Martínez et al39 showed the treatment of osteoblasts with PRP increased cell proliferation in the short term (15 days), and suggested the cell proliferation capacity diminished in the long term (30 days) because of cell exhaustion. The treatment with PRP also modified antigenic phenotype profile of cultured human osteoblasts by the expression of CD54, CD80, CD86, and HLA-DR antigens. The authors concluded that PRP treatment may accelerate bone neoplasia.

Plastic Surgery. Perhaps the most convincing evidence of the healing capacity of PRP has come from the field of plastic surgery. In a review on applications of platelet gel in facial plastic surgery, Bhanot and Alex40 reported that autologous PRP is especially useful for plastic and repair surgery of soft tissues, in which the positive effects of GFs are especially marked. In a study of 14 patients with soft tissue loss caused by recent trauma or chronic pathologies and treated by application of autologous fibrin-platelet glue and platelet gel, Valfonesi et al41 reported that besides accelerating healing, PRP reduces the risk of infection and length of hospital stay, with a corresponding saving in health costs. Furthermore, Man et al42 stated that PRP has also proven effective to arrest capillary bleeding in flap surgery after observing that the application of autologous platelet gel in 20 patients undergoing cosmetic surgery was effective in achieving and maintaining hemostasis during surgical procedures.

Trauma and orthopaedics. The application of PRP in trauma and orthopedic surgery remains highly controversial, despite numerous studies. Evidence remains sketchy on the biological diversity and on the platelet concentration required to achieve an accelerated response in bone. In some studies on bone grafts, PRP did not appear to increase bone formation.43-45 While this is consistent with a report in a canine model,46 in vitro studies showed that PDGFs stimulate the proliferation of human trabecular bone-forming cells.47 Importantly, Graziani et al48 reported that the effectiveness of PRP on the proliferative capacity of osteoblasts and fibroblasts in vitro depends on the specific concentrations used.

Recent in vitro research into the effects of PRP and its molecular components on cell proliferation and human macrophage migration revealed an inhibition of such migration.49 It showed a negative effect on healing, but positive stimulatory effects on osteoblasts, fibroblasts, and other cells. Platelet-rich plasma was found to be useful in human tendon and ligament repair by significantly increasing the proliferation of human tendinous cells and stimulating angiogenic factors, (eg, VEGF and hepatocyte-derived growth factor [HGF]).50,51 In knee surgery, autologous PRP injection facilitated anterior cruciate ligament reconstruction and enhanced re-anchorage of chondral fragments of > 2 cm by arthroscopy, obtaining complete and accelerated healing with a good functional outcome.51 Platelet-rich plasma injection in the common extensor tendon after suturing was also reported to aid in fiber reconstruction and relieve pain by different clinical assays.52

Ocular Surgery. Platelet-rich plasma, which has only been recently introduced into ocular surgery, has been reported to increase cell proliferation in wounds to the retina, improving outcomes in both in vitro and in vivo studies.27,53 Among other developments, this approach has also been used for peripheral nerve regeneration in rat models, obtaining highly favorable results from the application of platelet gel on nerve sutures.54

Gastroenterology. Studies have been conducted on the treatment of gastric ulcers in rats, reporting promising data on ulcer healing after an oral dose of human PRP.55

Skin Ulcers. Atri et al56 claimed that the use of autologous PRP improved the formation of granulation tissue in skin ulcer healing. Platelet-derived wound-healing factors began to be used in chronic leg ulcers with high collagen content and was found to stimulate vascularization and enhance connective tissue formation.57,58 The usefulness of PRP in pressure ulcer (PU) treatment remains under debate. Some authors concluded that the topical application of platelet lysates on ulcers has no effect on healing,59 whereas others found a higher percentage of healed surfaces in PUs and other skin ulcers treated with PRP.60 A platelet gel formed by a mixture of platelet concentrate and activated cryoprecipitate in the presence of calcium chlorides proved useful in treating a chronic ulcer on the foot of a diabetic patient, avoiding amputation.61

A study on venous leg ulcers demonstrated an increased expression of certain integrins after PDGF application, enhancing angiogenesis at sites of granulation.

**Keypoints**

- Encouraging outcomes have been obtained with platelet-rich plasma (PRP) therapy, including tissue regeneration, in multiple clinical settings.2,57
- Further research is required to establish the role of PRP in the treatment of tissue regeneration and to develop a standardized protocol for its preparation and application.
tissue formation and favoring the construction of new venous networks. Recently, Ramos-Torrecillas et al. suggested that PRP is an inexpensive and easily applied treatment for PUs, making this an alternative to traditional treatments.

Discussion

Encouraging outcomes, including tissue regeneration, have been obtained with PRP therapy in multiple clinical settings. However, its clinical applications have varied widely, and since the GFs participate in different physiological responses of the organism and tissues, PRP is a GF-rich source of general, rather than specific, usefulness to date. Furthermore, no common protocol has been developed for its preparation and application in regenerative therapy, especially in the treatment of ulcers, where the benefits of its topical application on ulcers remain controversial. In this case, 2 factors must be considered: the heterogeneity of ulcers (eg, vascular, pressure, diabetic) and the variety of GFs present in PRP. Therefore, the response to treatment may be expected to vary according to differences in ulcer characteristics and growth factor content in plasma. Further research is required to establish the role of PRP in the treatment of tissue regeneration and to develop a standardized protocol for its preparation and application.

Conclusion

There is wide scientific evidence on the positive role of PRP in tissue regeneration and wound healing. Also, a major advantage of autologous PRP in the clinical setting is that it has no adverse effects. The authors recommend further research is required to establish the exact role of PRP in the treatment of tissue regeneration and to develop a standardized protocol for its use.

References


