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## DENTISTRY &amp; MEDICINE

# Platelet-rich plasma

## Clinical applications in dentistry

NATHAN E. CARLSON, D.M.D. and  
ROBERT B. ROACH JR., D.D.S.

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## ▶ ABSTRACT

**Background.** Platelet-rich plasma, or PRP, has become a valuable adjunct in wound healing in dentistry. Postsurgically, blood clots initiate the healing and regeneration of hard and soft tissues. Clinicians and scientists are investigating the use of PRP in dentistry as a way to enhance the body's natural wound-healing mechanisms.

**Types of Articles Reviewed.** The authors reviewed scientific articles that discuss the basic knowledge of wound healing mechanisms and that directly studied the growth factors shown to be concentrated in PRP. They also reviewed articles written by clinicians and researchers in dentistry

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fields, including oral and maxillofacial surgery and periodontics to determine applications of PRP in the field of dentistry.

**Results.** All of the reviewed articles expressed promise in PRP use and in the growth factors expressed by the platelets concentrated in PRP—namely platelet-derived growth factor, or PDGF, and transforming growth factor- $\beta$ , or TGF- $\beta$ —as an adjunct to postsurgical wound healing. Both PDGF and TGF- $\beta$  have been shown in vivo to accelerate wound healing through different mechanisms. The development of an autologous PRP has been shown to be relatively easy, to be effective as a surgical adjunct, to retain high levels of the desired growth factors after preparation and to be clinically effective in accelerating postsurgical healing in both periodontal and oral surgery applications.

**Clinical Implications.** PRP has proven to be effective at improving surgical results in a variety of procedures in the field of oral and maxillofacial surgery. PRP also shows promise in periodontal regenerative therapy and should continue to be studied by scientists and clinicians alike.

Postsurgically, blood clots initiate the healing and regeneration of hard and soft tissues. Using platelet-rich plasma, or PRP, is a way to accelerate and enhance the body's natural wound-healing mechanisms. A natural blood clot contains mainly red blood cells, approximately 5 percent platelets and less than 1 percent white blood cells.<sup>1</sup> Platelets primarily are involved in wound healing through clot formation and the release of growth factors that initiate and support wound healing.

Using platelet-rich plasma is a way to accelerate and enhance the body's natural wound-healing mechanisms.

Using PRP involves taking a sample of a patient's blood preoperatively, concentrating autologous platelets and applying the resultant gel to the surgical site. This technique produces a blood clot that has nearly a reverse ratio of red blood cells and platelets compared with a natural clot. Surgical sites enhanced with PRP have been shown to heal at rates two to three times that of normal surgical sites.<sup>2</sup> Thus, PRP can be a great adjunct to many periodontal and oral surgical procedures such as bone grafts, implants and maxillofacial reconstructions.

## ► GROWTH FACTORS

Wound healing is a complex and growing science. Many cell types, growth factors and other proteins interact with one another to bring about timely and efficient repair of wounds. Researchers continue to study various growth factors to determine the actual role and mechanism of each growth factor in healing. On vessel injury and exposure of subendothelial tissue to blood (either due to accident or surgical manipulation), platelets begin to stick to exposed collagen proteins. Once platelets stick to collagen, they release granules containing adenosine diphosphate, serotonin and thromboxane, all of which contribute to the hemostatic mechanism and the clotting cascade. Additional platelets are drawn to the area and

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contribute to the formation of a platelet plug. The resultant plug is strengthened by an insoluble protein fiber meshwork known as fibrin that is formed as a result of the clotting cascade.<sup>3</sup>

This platelet plug and the initiation of the clotting cascade once were thought to be the extent of a platelet's role in wound healing. It now is known that platelets also actively extrude several growth factors involved in initiating and sustaining wound repair. The two most important of these growth factors are platelet-derived growth factor, or PDGF, and transforming growth factor- $\beta$ , or TGF- $\beta$ .

PDGF is chemotactic for polymorphonucleocytes, macrophages, fibroblasts and smooth muscle cells. PDGF also stimulates cell replication of important stem cells for fibroblasts and endothelial cells (increasing budding of new capillaries), stimulates production of fibronectin—a cell adhesion molecule used in cellular proliferation and migration during healing, including osteoconduction—and hyaluronic acid and helps bring about wound contraction and remodeling. TGF- $\beta$  stimulates fibroblast chemotaxis and the production of collagen and fibronectin by cells, while inhibiting collagen degradation by decreasing proteases and increasing protease inhibitors, all of which favor fibrogenesis.<sup>4,5</sup>

Each growth factor has the capability to induce a unique response in the enhancement of healing.

It has been shown that the topical application of these growth factors to healing sites can accelerate repair and wound maturation. One such study by Pierce and colleagues<sup>6</sup> examined the composition, quantity and rate of extracellular matrix deposition within growth factor-treated rabbit ear excisional wounds. Full-thickness, excisional punch biopsies were performed on a rabbit ear to bare cartilage. Individual growth factors were applied to wounds a single time, were followed and then were compared with control wounds that had no growth factor added to them. Researchers found that PDGF accelerated wound closure primarily through augmenting connective-tissue matrix deposition at the leading edge of new granulation tissue. New collagen accumulation did not occur until later in the healing process. Thus, this study indicated that PDGF accelerates early wound closure primarily via enhanced glycosaminoglycan, hyaluronic acid and fibronectin deposition. TGF- $\beta$ , on the other hand, stimulated new collagen deposition and maturation into large bundles at the leading edge of the wound, creating a mature fibroblastic wound directly and likely bypassing some of the acute inflammatory phase of wound repair.<sup>6</sup>

It also has been demonstrated that PDGF and TGF- $\beta$  specifically stimulated significant new granulation tissue in vivo, thus suggesting their importance in the healing of full-thickness dermal wounds.<sup>7</sup> Again, it was noted that each growth factor has the capability to induce a unique response in the enhancement of healing, especially having inductive effects on cells entering the wound.

## PLATELET-RICH PLASMA

The study of these growth factors combined with the discovery of their extrusion by platelets has led to the development of an autologous platelet gel—PRP—to be used in various surgical fields such as otolaryngology, head and neck surgery, neurosurgery, general surgery, oral and maxillofacial surgery, and periodontics. Whitman and colleagues<sup>8</sup> have called PRP an "autologous alternative to fibrin glue." Fibrin glue obtained through blood bank donations has been used for years as a hemostatic agent and surgical adhesive. The important difference in composition between PRP and fibrin glue is the presence of a high concentration of platelets and native concentration of fibrinogen in PRP. The platelets in PRP, once activated by the addition of thrombin, begin to release the growth factors PDGF and TGF- $\beta$ , as well as many others that serve to accelerate the wound-healing process.<sup>8</sup> Thus, PRP can serve both in hemostasis and adhesion of graft material, as well as contribute physiologically to more rapid healing of the surgical site.

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Numerous techniques have been put forth for the immediately preoperative development of autologous PRP.<sup>8-11</sup> Most are quite similar and only variations on a theme. In a technique described by Whitman and colleagues,<sup>8</sup> one unit of whole blood (approximately 450 milliliters) is drawn into a standard collection bag containing a citrate-phosphate-dextrose anticoagulant. The blood first is centrifuged at 5,600 rotations per minute, or rpm, to separate the platelet-poor plasma from the erythrocytes, platelets and leukocytes. The centrifuge speed then is slowed to 2,400 rpm to allow for further separation of the platelets and leukocytes from the red blood cell pack. Removal of this red blood cell pack yields 30 mL of plasma with the concentrated platelets. Platelet counts in this PRP often range from 500,000 to 1 million.

The resultant PRP is stored at room temperature until the surgical team is ready to use it. Once the team is ready, the clinician prepares a mixture of 10,000 units of bovine thrombin in powder form and 10 mL of 10 percent calcium chloride. Next, 7 mL of PRP and 2 mL of air are drawn into a 10-mL syringe. One mL of the thrombin/calcium-chloride mixture then is aspirated into the syringe and gently rocked to allow the air bubble to mix the components. Within five to 30 seconds, a gel is formed as the citrate is neutralized and the thrombin activates polymerization of the fibrin and degranulation of the platelets. The gel then is injected into the surgical field as required.

Marx and colleagues<sup>2</sup> used a similar technique to prepare PRP and discussed its use in the enhancement of bone-graft procedures. The purpose of their study was threefold. The first purpose was to document that PRP does increase platelet concentration when placed into grafts, that PRP contributes to the presence of PDGF and TGF- $\beta$ , and that cancellous bone marrow grafts do have receptors for these growth factors. The second purpose was to determine the ability of PRP to increase the rate of bone formation in a graft and to enhance the density of the bone as measured at six months. Finally, the authors wanted to present a model of bone regeneration with grafting that illustrated the mechanism by which PRP enhances the rate and amount of healing.

The exact mechanisms of action of the various players in components of wound healing are not fully understood yet.

The researchers selected from among human subjects 88 mandibular continuity defects of greater than 5 centimeters that arose from tumor extirpations without radiotherapy that were to be treated with cancellous cellular bone marrow grafts. The defects were randomly assigned to one of two groups; one group received PRP-enhanced grafts, and the other group received bone grafts without PRP. Samples of PRP and venous blood were submitted at the time of surgery for study. The bone grafts were evaluated radiographically at two, four and six months after surgery. At six months, endosseous implants were placed using a technique that allowed for the removal of a 4-mm core bone specimen for evaluation.

Monoclonal antibody studies revealed the presence and retention of both PDGF and TGF- $\beta$  in the PRP preparation. A similar study of the bone harvested at the time of the implant placement confirmed the presence of receptors to PDGF and TGF- $\beta$ , especially around blood vessels in a perivascular sheet. Platelet counts of PRP and control blood measured 338 percent more platelets in the PRP than in the control blood. In the radiographic assessment, grafts with the PRP were assessed consistently at or up to twice their actual maturity. A histomorphometric study of the bone samples taken at six months showed increased trabecular bone density for PRP grafts compared with control grafts. All of these results together strongly suggest that adding PRP to bone grafts accelerates the rate of bone formation and the degree of bone formation in bone grafts at least during the first six months.<sup>2</sup>

Whitman and colleagues<sup>8</sup> mentioned several oral surgery procedures in which PRP has been a valuable adjunct; they include ablative surgical procedures, mandibular reconstruction and surgical repair of alveolar cleft and associated oroantral or oronasal fistulas, as well as in procedures relating to the placement of osseointegrated implants. In these procedures, the adhesive nature of PRP enables easier handling of graft material, more predictable flap adaptation and hemostasis, and a more predictable seal than with primary closure alone. Also present is the resultant release of the previously mentioned growth factors. Kassolis and colleagues<sup>12</sup> reported that the successful use of PRP-augmented demineralized freeze-dried bone allografts for alveolar augmentation or sinus lift procedures before implant placement.

In the field of periodontics, researchers are studying PDGF for its use as an adjunct to regenerative therapy. Cho and colleagues<sup>13</sup> first attempted to identify the cell type and source that were most active in regenerative therapy so they could select the most appropriate and functional growth factors to use for stimulating periodontal regeneration. The early recruitment and rapid repopulation of progenitor cells from the periodontal ligament were regarded as critical events for successful regeneration. Next, Cho and colleagues studied the effects of PDGF, TGF- $\beta$  and other growth factors in vitro and in vivo. They found that PDGF was the only growth factor that effectively stimulated periodontal ligament fibroblast migration and proliferation without the added risk of the patient experiencing ankylosis of the teeth. When used in clinical trials on beagles, PDGF-modulated guided tissue regeneration, or GTR, therapy was shown to effectively aid in the regeneration of periodontal furcation defects.

Park and colleagues<sup>14</sup> conducted similar studies on beagles, comparing treatment of Class III furcation defects with PDGF and GTR vs. with GTR alone. The study indicated a statistically greater amount of bone and periodontal ligament in sites treated with PDGF and GTR together than in sites treated with GTR alone. The newly formed bone filled 80 percent of the lesion at eight weeks and 87 percent of the lesion at 11 weeks in the sites treated with PDGF and GTR, compared with 14 percent of the lesion at eight weeks and 60 percent at 11 weeks in sites treated with GTR alone. Additionally, the sites treated with PDGF and GTR seemed to have increased ratios of wanted to unwanted tissue types filling the wounds as compared with sites treated with GTR alone.

## ▶ CONCLUSION

The field of transfusion medicine, as it applies to wound healing and the formation of an autogenous platelet gel, still is a young scientific field in which many discoveries are yet to be made. The exact mechanisms of action of the various players in components of wound healing are not fully understood yet. Ideal ratios of the components of PRP preparations still are being investigated, and more clinical research with long-term results is needed. In 2000, commercially available PRP-processing systems cost approximately \$9,000 and the disposable kit cost \$230 per patient. With the current competitive market, the same PRP processing system can now be purchased for \$5,900. With the reduction in cost, further clinical research and clinical use should become more cost beneficial (Tim Dugan, CoMedical, specialty representative, personal communication, May 2002).<sup>15</sup>

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## ▶ FOOTNOTES

Dr. Carlson is a 12-month advanced general dentistry resident, U.S. Army Dental Corps, Fort Lewis, Wash.

When this article was written, Dr. Roach was staff, Oral and Maxillofacial Surgery, resident mentor, Madigan Army Medical Center, U.S. Army Dental Corps, Fort Lewis, Wash. He now is assistant chief, Oral and Maxillofacial Surgery Residency, Brooke Army Medical Center, San Antonio. Address reprint requests to Dr. Roach at 1715 Palmer View, San Antonio, Texas 78258, e-mail "[Robert.Roach@CEN.AMEDD.ARMY.MIL](mailto:Robert.Roach@CEN.AMEDD.ARMY.MIL)".

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