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Platelet-Rich Plasma: Evidence to Support Its Use

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Platelet-rich plasma (PRP) is an autologous concentration of human platelets in a small volume of plasma. Therefore, the term PRP is preferred to autologous platelet gel, plasma-rich growth factors (PRGFs), or a mere autologous platelet concentrate. Because it is a concentration of platelets, it is also a concentration of the 7 fundamental protein growth factors proved to be actively secreted by platelets to initiate all wound healing. These growth factors include the 3 isomeres of platelet-derived growth factor (PDGF$\alpha\alpha$, PDGF$\beta\beta$, and PDGF$\alpha\beta$), 2 of the numerous transforming growth factors-β (TGFβ1 and TGFβ2), vascular endothelial growth factor, and epithelial growth factor. All of these growth factors have been documented to exist in platelets.[1,2] Because these concentrated platelets are suspended in a small volume of plasma, PRP is more that just a platelet concentrate; it also contains the 3 proteins in blood known to act as cell adhesion molecules for osteoconduction and as a matrix for bone, connective tissue, and epithelial migration. These cell adhesion molecules are fibrin itself, fibronectin, and vitronectin.

PRP development via centrifugation has been greatly simplified so that it can be used in the office setting as well as the operating room. However, the centrifugation process must be sterile and precisely suited to platelet separation from red blood cells and their sequestration in high concentrations without lysing the platelets or damaging them so that they no longer can actively secrete their growth factors. Therefore, not all currently marketed PRP devices are equal; some do not concentrate viably active platelets in sufficient numbers to produce a healing enhancement. This has led to and explains most of the criticisms regarding the efficacy of PRP. In addition, there have been some research efforts to study PRP in animal models that have a blood volume that is too small to produce PRP; therefore, these studies have used donor blood. This of course is homologous, not autologous, and therefore is not true PRP. The use of donor animal blood platelets imparts an overt immune reaction and leads to false-negative results that may falsely be ascribed to PRP.

True PRP is always autologous and is not homologous. An example of this confusion is the use of lyophilized donor platelets. Homologous platelets are not viable and could not possibly secrete bioactive growth factors. Homologous platelets are also antigenic due to their abundance of cell membranes. Certainly, antiplatelet antibodies could develop from this product and second set reactions would follow. Such substances offer no useful comparison to PRP.

Regarding autologous PRP, clinicians must read the literature and assess the results of studies relating to PRP as to whether a Food and Drug Administration (FDA)-cleared device produced the PRP and whether platelet concentrations and growth factors were documented. At the time of this writing, only 2 office devices used to develop PRP have been cleared by the FDA (Smart PReP; Harvest Technologies Inc, Plymouth, MA; and the Platelet Concentration Collection System [PCCS]; 3i Implant Innovations, Inc, West Palm Beach, FL).[2] A study conducted in our laboratories and repeated by the Center for Blood Research in Boston, MA, indicated that of all of the devices tested, these 2 FDA-cleared PRP devices produced the greatest platelet concentrations and, most important, release of a therapeutic level of bioactive growth factors (Tables 1 and 2). Studies suggesting that there is no benefit from PRP can often be traced to poor-quality PRP produced by inadequate devices. Studies by Weibrich and Klies,[3] for instance, documented the inadequacy of such devices. They found this one particular device to be deficient in developing therapeutic levels of platelets compared with other devices and was not cleared by the Certification Europe organization, which is the European counterpart to the US

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Table 1. GROWTH FACTOR YIELDS PER DEVICE

Device	Mean PRP Volume (mL)	PDGF-$\alpha\beta$ (ng/mL)	TGF-β (ng/mL)
Laboratory Centrifuge (Anitua Protocol)[26]	9.5 ± 4.1	35 ± 11.3	52 ± 7.6
Laboratory Centrifuge (Landesberg Protocol)[27]	10.6 ± 2.4	26 ± 13.7	50 ± 10.8
Clinaseal Sealed Technology Centrifuge*	7.6 ± 1.5	46 ± 15.3	55 ± 18.7
ACE Surgical†	7.8 ± 0.6	35 ± 17.2	43 ± 17.9
AG Curasan‡	7.6 ± 1.5	39 ± 11.4	39 ± 16.4
3i PCCS	7.0 ± 1.5	103 ± 27	144 ± 31.1
Harvest Technologies "SmartPReP"	7.4 ± 0.5	133 ± 29.2	170 ± 42.3

*Clinaseal Sealed Technology Centrifuge; Salvin Dental Specialties Inc, Charlotte, NC.
†ACE Surgical, Brockton, MA.
‡AG Curasan, Kleinostheim, Germany.

FDA. Our own testing concurs with their findings. Therefore, the clinician must look at such PRP-negative literature to assess whether PRP with therapeutic platelet levels was really used.

The prudent clinician who uses PRP or the clinician judging whether the healing enhancement of PRP would offer a benefit to his or her patients should assess the literature with scientific scrutiny and ask the following critical questions.

How Does PRP Work?

PRP works via the degranulation of the α granules in platelets, which contain the synthesized and prepackaged growth factors. The active secretion of these growth factors is initiated by the clotting process of blood and begins within 10 minutes after clotting. More than 95% of the presynthesized growth factors are secreted within 1 hour.[2] Therefore, PRP must be developed in an anticoagulated state and should be used on the graft, flap, or wound, within 10 minutes of clot initiation. Studies that have not used anticoagulated whole blood, which is then clotted to activate the PRP, are not really studies of PRP and therefore are misleading. Related to this, PRP has been shown to remain sterile and the concentrated platelets viable for up to 8 hours once developed in the anticoagulated state and placed on a sterile surgical table. Like most growth factors such as bone morphogeneic protein (BMP) and similar to collagen, the growth factors within the α granules of platelets are incomplete because they must be soluble. As the clotting process activates the platelets, the growth factors are secreted from the cell through the cell membrane. In this process, the α granules fuse to the platelet cell membrane where the protein growth factor is completed to a bioactive state by the addition of histones and carbohydrate side chains to these proteins. Therefore, platelets damaged or rendered nonviable by PRP processing will not secrete bioactive growth factors and may result in disappointing outcomes.

The secreted growth factors immediately bind to the external surface of cell membranes of cells in the graft, flap, or wound via transmembrane receptors. Studies have shown that adult mesenchymal stem

Table 2. PLATELET YIELDS PER DEVICE

Device	Mean PRP Volume (mL)	Mean Platelet Concentration $\times 10^3$	Platelet Yield (%)	Increase Above Baseline (%)
Laboratory Centrifuge (Anitua Protocol)[26]	9.5 ± 4.1	433 ± 129	35 ± 168	190
Laboratory Centrifuge (Landesberg Protocol)[27]	10.6 ± 2.4	336 ± 141	30 ± 10.3	150
Clinaseal Sealed Technology Centrifuge*	7.6 ± 1.5	401 ± 267	39 ± 16.3	164
ACE Surgical†	7.8 ± 0.6	493 ± 245	33 ± 10.2	180
AG Curasan‡	7.6 ± 1.5	344 ± 192	29 ± 14.1	139
3i PCCS	7.0 ± 1.5	939 ± 284	61 ± 8.9	324
Harvest Technologies "SmartPReP"	7.4 ± 0.5	1,086 ± 227	62 ± 4.4	404

*Clinaseal Sealed Technology Centrifuge; Salvin Dental Specialties Inc, Charlotte, NC.
†ACE Surgical, Brockton, MA.
‡AG Curasan, Kleinostheim, Germany.

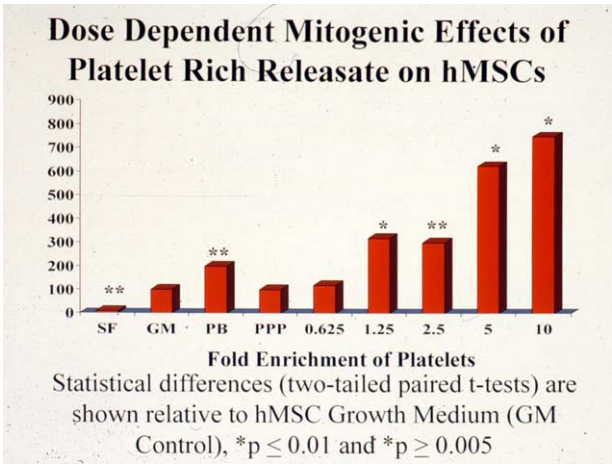

FIGURE 1. Proliferation of human mesenchymal stem cells (hMSCs) is proportional to platelet concentrations in PRP. (SF, fetal calf serum; GM, growth medium; PB, phosphate buffer; PPP, platelet poor plasma.)

cells, osteoblasts, fibroblasts, endothelial cells, and epidermal cells express the cell membrane receptors to growth factors in PRP.[1] These transmembrane receptors in turn induce an activation of an endogenous internal signal protein, which causes the expression of (unlocks) a normal gene sequence of the cell such as cellular proliferation, matrix formation, osteoid production, collagen synthesis, etc. The importance of this knowledge is that the PRP growth factors never enter the cell or its nucleus, they are not mutagenic, and they act through the stimulation of normal healing, just much faster. Therefore, PRP has no ability to induce tumor formation and has never done so.[4,5]

After the initial burst of PRP-related growth factors, the platelets synthesize and secrete additional growth factors for the remaining 7 days of their life span. Once the platelet is exhausted and dies off, the macrophage, which has arrived in the region via the vascular in-growth stimulated by the platelets, assumes the function of wound healing regulation by secreting some of the same growth factors as well as others. Therefore, the number of platelets in the blood clot within the graft, wound, or adherent to a flap sets the rate of wound healing. PRP merely increases this number.

How Many Platelets are Enough?

This question has been elegantly answered by the work of Haynesworth et al,[6] who showed that the proliferation of adult mesenchymal stem cells and their differentiation were directly related to the platelet concentration. They showed a dose-response curve, which indicated that a sufficient cellular response to platelet concentrations first began when a 4- to 5-fold increase over baseline platelet numbers was achieved (Fig 1). A similar study by Lui et al[7] showed that fibroblast proliferation and type I collagen production were also enhanced by increasing platelet concentrations and that much of the response was pH dependent with the best responses occurring at more acidic pH levels. Together these studies not only documented the necessity of devices to concentrate sufficient platelets but also explained both the enhanced bone regeneration results associated with PRP and the enhanced soft tissue results. Because most individuals have a baseline blood platelet count of 200,000 ± 75,000/μL, a PRP platelet count of 1 million/μL as measured in the standard 6-mL aliquot has become the benchmark for "therapeutic PRP." The importance of this knowledge is that our studies have indicated that only the aforementioned FDA-cleared devices consistently achieve this therapeutic level of platelet concentration and hence growth factor release (Tables 1 and 2).

Does PRP Really Work?

The vast majority of publications report a significant enhancement of healing when PRP is used. Some of these publications that report positive results in either or both bone and soft tissue healing are Marx et al,[1] with autogenous mandibular bone grafts; Garg,[8] with composites of autogenous bone grafts and bone substitutes in sinus lifts and other surgeries; Man et al,[9] with cosmetic surgeries; Adler and Kent,[10] specifically with face lift surgeries; Camargo et al,[11] with intrabony periodontal defects; Kim et al,[12] with periimplant defects; Kassolis et al,[13] with freeze-dried bone allografts in sinus lift surgeries; Abuzeni and Alexander,[14] with cosmetic dermal fat grafts; and Monteleone et al,[15] with skin graft healing enhancement. These studies document the observed enhancement of bone regeneration as well as the enhancement of soft tissue healing. However, there have also been publications that concluded that there was little or no benefit from PRP: Froum et al,[16] with sinus lift grafts; Aghaloo et al,[17] with cranial defects in rabbits; and Shanaman et al,[18] in ridge augmentations together with demineralized freeze-dried bone allografts. How does the reader then reconcile these apparently conflicting publications? The best way is to review the level of science each publication represents, assessing the quality of PRP used in each study and the controls used.

If the reader analyzes some of the aforementioned articles, they see that articles purporting little benefit from PRP often do not use real PRP, use damaged platelets, may have not activated the platelets, or have

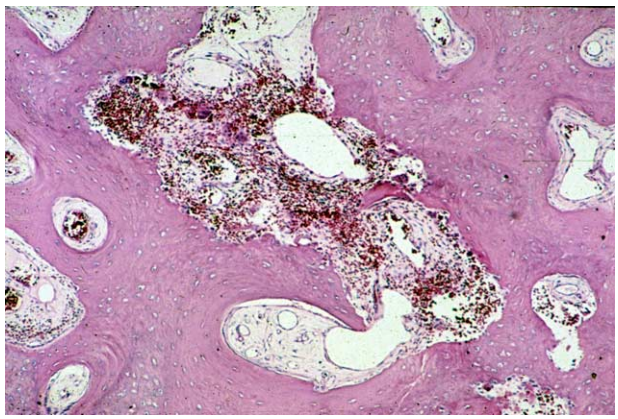

FIGURE 2. Human bone graft histology at 4 months without platelet-rich plasma. There is a 59% trabecular bone density, active resorption remodeling, and a preponderance of immature bone (hematoxylin and eosin stain, original magnification ×4).

statistically insufficient data to draw a valid conclusion. An example is the article by Froum et al.[16] This study included only 3 patients and introduced multiple independent variables to confound their results. One patient received only anorganic bovine bone and a BioGide membrane (Luitpold/Osteohealth, Shirley, NY) with PRP; another patient received anorganic bovine bone with 5% autogenous bone, a BioGide membrane, and PRP; and the third received only anorganic bovine bone and a Gore-Tex membrane (W.L. Gore and Associates, Flagstaff, AZ) with PRP. In 1 case, immediate "test" implants were also placed that were not placed in the other 2. In addition, this study reported using "a large draw Metronic unit" (Tempe, AZ) and did not test the platelet concentrations as in other studies. Although studies such as this are often referenced and quoted as showing little PRP benefit, their conclusions cannot be accepted as valid, particularly if judged against the studies by Marx et al,[1] in which 88 patients were used with strict controls; by Adler and Kent,[10] in which 20 patients were used with split side controls and platelet counts were documented; in Camargo et al,[11] in which 18 patients were used with identical techniques and materials in a split mouth design; and in Monteleone et al,[15] in which 20 patients were used in a side-by-side, same patient–control design of skin graft donor sites. All of these studies concluded a profound enhancement by PRP.

Another study often quoted or referenced as showing little benefit from PRP is the study by Aghaloo et al.[17] Their study used non–critical-sized defects in the New Zealand White rabbit model. Their results showed no benefit of PRP alone in the defect but actually showed significant enhancement when PRP was combined with autogenous bone compared with autogenous bone alone. This finding is consistent with those of Marx et al,[1] Garg,[8] and others and is actually a study supporting the use of PRP if read in its entirety. Similarly, the study by Shanaman et al[18] is frequently quoted as showing no positive results with PRP related to their study of only 3 patients for ridge augmentation, yet the authors specifically state in their discussion, "The histologic observations suggest that PRP in combination with DFDBA [demineralized freeze-dried bone allografts] and covered with a barrier membrane supports new bone formation." In addition, the core biopsy photomicrographs of PRP-enhanced grafts from this study show "significant new bone formation," and the clinical photographs of the ridges as described by the authors showed "extensive defect fill with a hard bone-like material within the defect area observed." The confusion about the interpretation of this study as being positive or negative toward PRP once again relates to the science or nonscience of this study. This was not a study per se but rather a case report of only 3 cases without any controls. The documentation presented by the authors was stated to be and was shown to be a bone regeneration enhancement with PRP. Yet the authors perhaps inadvertently implied a negative PRP interpretation when they stated, "The results of this case series appear comparable to other GBR [guided-bone regeneration] studies without the use of PRP." The reader should now see the value of statistically significant numbers as opposed to a "case series" of just 3 cases. The reader should also appreciate the use of study controls versus no controls and that the use of the word "appear" is a poor substitute for controlled data.

Perhaps the best proof of the absolute clinical efficacy and value of PRP can be seen directly in the published photographs of bone grafts at 4 months

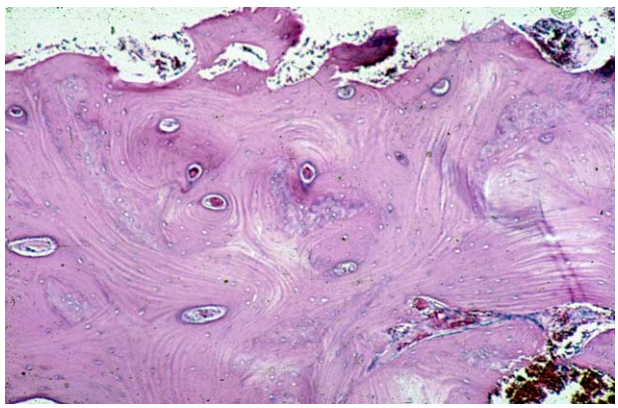

FIGURE 3. Human bone graft histology at 4 months with platelet-rich plasma enhancement. There is an 80% trabecular bone density, the bone is mature, and there is no evidence of active resorption remodeling (hematoxylin and eosin stain, original magnification ×4).

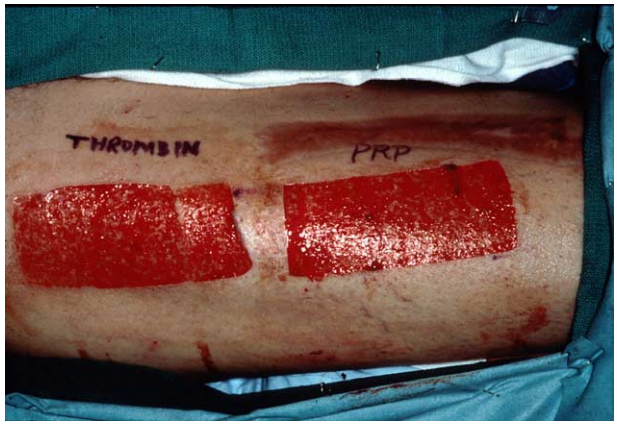

FIGURE 4. Split-thickness skin graft donor sites at 0.016 inch in depth comparing a control site with a platelet-rich plasma–treated site at the time of initial placement. Note the old skin graft donor site above the platelet-rich plasma–treated site is scarred, contracted, and hyperpigmented.

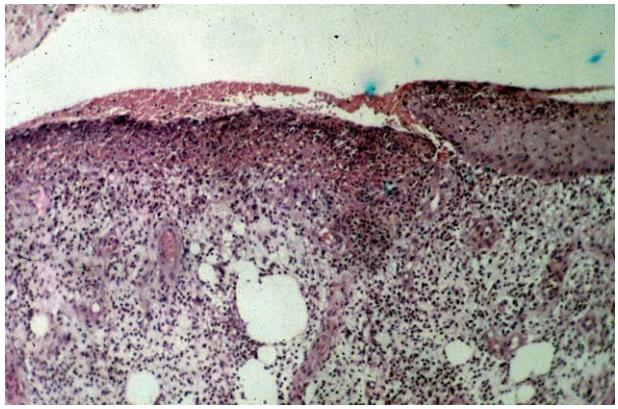

FIGURE 6. Histology specimen of the split-thickness skin graft donor site control at 6 days. There is no epithelial budding, and the connective tissue shows macrophages and young plump fibroblasts without significant collagen production (hematoxylin and eosin stain, original magnification ×10).

without PRP versus those with PRP (Figs 2, 3) and the photographs of skin healing at various stages without PRP in contrast to skin healing with PRP (Figs 4, 5). Figure 2 represents an autogenous bone graft healing at 4 months without PRP. It has a 59% trabecular bone density, and 70% of that bone is in an immature stage as evidenced by a random pattern of large osteocytic lacunae without lamellar architecture. Only 30% has lamellar architecture, indicating that the graft itself primarily remains within a resorption-remodeling cycle as also evidenced by osteoclastic resorption. By contrast, Figure 3 represents a size- and age-matched autogenous bone graft healing at 4 months with PRP. This histology has 80% trabecular bone density, and 85% of that bone is in a mature state as evidenced by lamellar architecture and smaller osteocytic lacunae as well as mature haversian systems. There also is no evidence of active resorption and remodeling, indicating a level of stable maturity.

Figures 4 and 5 represent side-by-side controlled split-thickness skin graft donor sites of 0.016 inch in depth at the time of their placement and after 6 days of healing. This dramatic side-by-side comparison represents "seeing is believing" evidence. The graft site without PRP in Figure 5 has peripheral erythema and abundant granulation tissue with only 5% or less epithelialization seen at the edges. The graft site of the same size and depth and on the same individual at 6 days with PRP use has no peripheral erythema and already has a 95% thin epithelial covering. This is further proved by histology specimens from each of these 2 sites taken at 6 days (Figs 6, 7). The non-PRP histology shows no epithelial budding and granula-

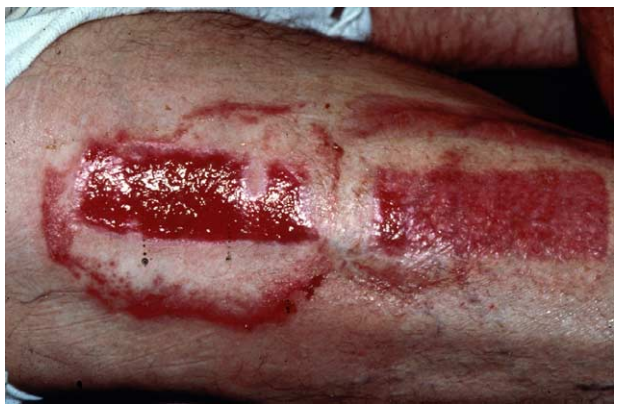

FIGURE 5. The same split-thickness skin graft donor sites as seen in Figure 4 now at 6 days. The control site has a peripheral erythema and is covered by granulation tissue. There is minimal epithelialization. The platelet-rich plasma–treated site has no peripheral erythema. The granulation tissue has already been replaced by a thin epithelial cover at this early stage.

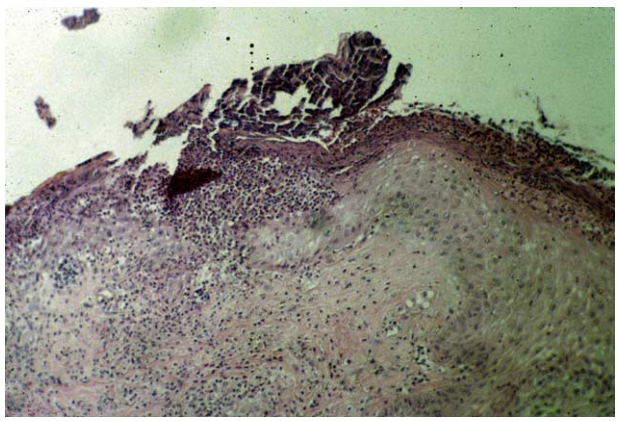

FIGURE 7. Histology specimen of split-thickness skin graft donor site treated with platelet-rich plasma at 6 days. Prominent epithelial budding is noted and the underlying connective tissue shows a mature dermis development with collagen deposition (hematoxylin and eosin stain, original magnification ×10).

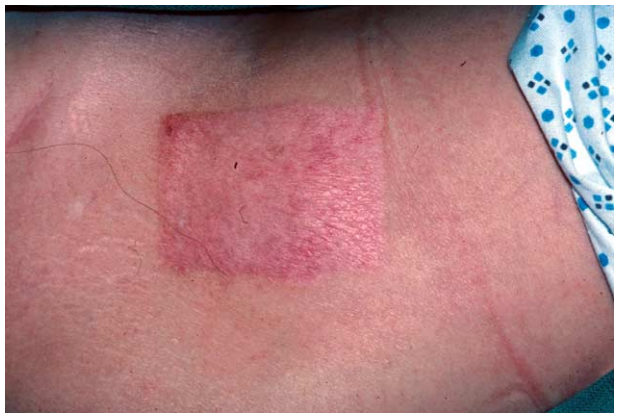

FIGURE 8. Split-thickness skin graft donor site control of 0.016 inch in depth at 45 days. Note the abundant subsurface vascularity indicative of a thin epithelial cover and the persistence of the hypervascular phase of healing, which represents an immaturity of the healing process.

tion tissue consisting only of macrophages and plump young fibroblasts. The PRP-treated site instead shows obvious epithelial budding and a mature dermis beneath. Figures 8 and 9 show another individual's split-thickness skin graft donor sites at 45 days without PRP and with PRP, respectively. Note the dense subsurface vascularity of the non-PRP site, which is indicative of a thin epithelial cover and incomplete healing. Note the absence of such subsurface vascularity at the PRP site, indicative of the involution of this vascular phase of healing, the greater thickness of the epithelial cover, and a more advanced healing. Finally, Figure 10 shows the individual side-by-side donor sites of Figure 4, now at 6 months. It is evident that the site without PRP has more scarring and a greater loss of pigmented cells than the PRP site, indicating that the PRP effect of faster and more complete healing reduces scar and promotes a greater melanocyte survival.

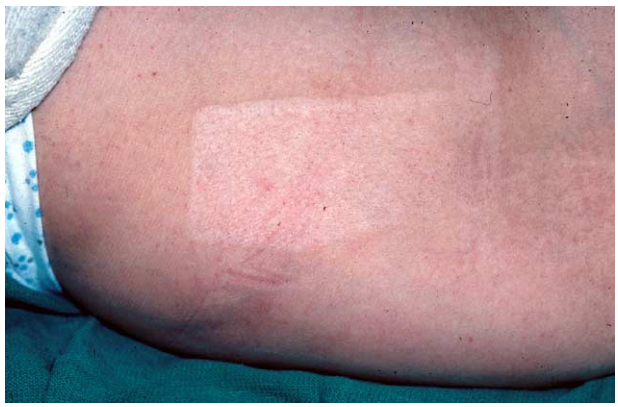

FIGURE 9. Split-thickness skin graft donor site of 0.016 inch in depth in the same patient treated with platelet-rich plasma at 45 days. Note the absence of subsurface vascularity indicative of a more mature healing process and a greater thickness of the overlying epithelium.

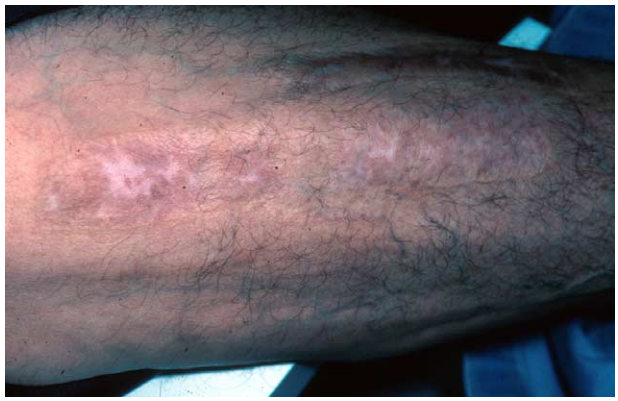

FIGURE 10. The split-thickness skin graft side-by-side donor sites from Figures 4 and 5 seen now at 6 months. Note that the control side has more scarring, is contracted, and has a greater variation in pigmentation.

What Clinical Situations Benefit from PRP?

Because PRP enhances osteoprogenitor cells in the host bone and in bone grafts,[1,19] it has found clinical applications in fully autogenous bone grafts and composites of autogenous bone grafts with a variety of bone substitutes with as little as 20% autogenous bone.[8] Therefore, PRP has shown improved results in continuity defects,[1,20] sinus lift augmentation grafting,[13,21] horizontal and vertical ridge augmentations,[8] ridge preservation grafting,[22] and periodontal/peri-implant defects.[12] We have also observed PRP to allow earlier implant loading and improved osseointegration when used in compromised bone such as osteoporotic bone and bone after radiotherapy. Because PRP also enhances soft tissue mucosal and skin healing, it is used in connective tissue grafts, palatal grafts, gingival grafts, mucosal flaps together with Alloderm (BioHorizons, Birmingham, AL) for root coverage, skin graft donor and recipient sites, dermal fat grafts, face lifts, blepharoplasty, and laser resurfacing surgery.

What is the Safety of PRP?

Because it is an autogenous preparation, PRP is inherently safe and therefore free from concerns over transmissible diseases such as HIV, hepatitis, West Nile fever, and Cruetzfeld-Jacob disease (CJD) ("mad cow disease"). It therefore is also well accepted by patients. Related to the issue of CJD, concerns have been advanced about the use of bovine thrombin as the clotting initiator. However, bovine thrombin has a

completely negative history of CJD in more than 10 million uses in a wide variety of surgeries worldwide. Because the transmission vector of CJD is a prion that to date has been found only in neural tissues of the central nervous system in cattle, sheep, cats, humans, etc and because bovine thrombin is derived solely from blood and is also heat processed for purification, it remains in standard use today in many surgeries and is the safe initiator of clotting related to PRP.

Of more reasonable clinical concern are the rare cases where bovine thrombin was used as a hemostatic agent in open orthopedic, neurosurgical, and cardiovascular surgeries and later bleeding episodes were encountered.[23,24] Although less than 20 such cases have been reported, these adverse events have been thoroughly investigated. The second set bleeding episodes in these patients were not due to antibodies against bovine thrombin or human thrombin but instead due to antibodies that developed to bovine factor Va that was a contaminant in certain bovine thrombin commercial preparations.[23-25] These antibodies, which developed to bovine factor Va, cross-reacted with human factor Va and thereby produced coagulopathies and these rare bleeding episodes. Since 1997, the processing of bovine thrombin by Gentrac (Jones Medical Industries, St Louis, MO) has eliminated contamination of bovine thrombin with bovine factor Va from pre-1997 levels of 50 mg/mL to less than 0.2 mg/mL and thus no further cases related to this specific preparation have been reported.[25] In addition, the bovine thrombin preparations used in the reported cases were high dose (>10,000 units) and were applied directly onto open wounds where absorption into the systemic circulation is certain. The use of bovine thrombin in PRP is low dose (<200 units), is topical with no entry into the systemic circulation, and is already clotted when it comes into contact with human tissues. It is therefore not absorbed systemically but is engulfed and digested by the macrophages that also digest the clot itself.

Does PRP Promote Infections?

Some have empirically suggested that PRP may promote infections due to the flawed logic that it is a blood clot and that blood agar is used in microbiology laboratories to culture bacteria. However, PRP is no different in substrate than the blood clot that forms in every wound and therefore could not support bacterial growth any more than any other blood clot. In fact, PRP has a pH of 6.5 to 6.7 compared with a mature blood clot of 7.0 to 7.2. It has thus been countersuggested that PRP actually inhibits bacterial growth. To this end, no clear studies or data are available. Our experience comparing similar bone grafts and skin wounds with and without PRP shows no promotion or inhibition of infection complications. Each has an incidence of 2.0% to 3.5%. However, the clinician should know that preparation of PRP must use an aseptic technique.

Is the Value of PRP Limited to Soft Tissue?

Some have also implied that the value of PRP is mostly related to soft tissue healing enhancement because platelets do not contain BMP. Indeed, PRP does not contain any BMP and it is not osteoinductive. However, all bone graft healing and osteoconduction into bony defects and around the numerous bone substitutes used today arise from adult mesenchymal stem cells and their lineage, leading to osteoblasts, all of which have already been proved to respond to PRP with accelerated bone formation.[1,6,26] In fact, the first randomized trial of PRP versus non-PRP grafts focused specifically on and documented PRP's enhancement of bone formation[1] (Figs 3, 4).

Today, PRP remains the sole growth factor preparation available to oral and maxillofacial surgeons and other specialties of dentistry for outpatient use. The recent withdrawal of the application for FDA approval of recombinant human BMP-2 (rhBMP-2) for craniofacial, oral surgical, and dental applications is a disappointment to the entire profession but underscores the value of PRP. The value of PRP is its proven effectiveness, its safety, its cost effectiveness, and its availability in an easy-to-develop manner and its FDA approval if developed by an FDA-cleared device.

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