Case Series

# Alveolar Ridge and Sinus Augmentation Utilizing Platelet-Rich Plasma in Combination With Freeze-Dried Bone Allograft: Case Series

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***Background:*** *Alveolar bone regeneration is frequently necessary prior to placement of implants. Efforts to improve wound healing have focused on factors that may enhance bone formation following guided bone regeneration (GBR) techniques alone or in combination with bone replacement graft materials. Recent reports suggest that platelet-rich plasma (PRP), presumably high in levels of peptide growth factors, may enhance the formation of new bone when used in combination with autogenous graft material.*

***Methods:*** *In this report, the clinical and radiographic results are presented on 15 consecutively treated patients using autologous PRP in combination with freeze-dried bone allograft (FDBA) for sinus elevation and/or ridge augmentation. FDBA and PRP (0.5 g/2cc PRP) were mixed and placed as a composite graft material. A gel formed by mixing autologous thrombin-rich plasma with PRP (1:4 ratio) was used to cover the graft material. Core biopsies of grafted areas were obtained in several patients as part of implant site preparation and were evaluated histologically to determine site maturation.*

***Results:*** *Of 36 implant fixtures, 32 (89%) were considered clinically successful demonstrating complete bone coverage of the implant, no mobility, and a normal radiographic appearance at the time of re-entry and 12 months post-implant exposure. Four implants were removed due to mobility at the time of surgical exposure. Histologic evaluation of biopsy specimens revealed numerous areas of osteoid and bone formation around FDBA particles, with no evidence of inflammatory cell infiltrate.*

***Conclusions:*** *These clinical and histological findings suggest that ridge augmentation and sinus grafting with FDBA in combination with PRP provide a viable therapeutic alternative for implant placements. Future studies are necessary to determine whether PRP enhances new bone formation or maturation with bone replacement allografts.* J Periodontol 2000; 71:1654-1661.

**KEY WORDS**

**Grafts, bone; maxillary sinus/surgery; plasma, platelet-rich; alveolar ridge augmentation; guided bone regeneration; wound healing.**

Guided bone regeneration (GBR) has enabled the placement of implants in sites that are deficient in either bone quantity or quality. Two areas of particular concern have been the maxillary sinus and thin alveolar ridges. Successful bone regenerative outcomes have been achieved by a variety of GBR techniques including the use of membranes alone,[1-4] bone replacement grafts,[5-7] and combination therapies.[8]

Considerable attention has focused on the potential application of growth and differentiation factors to enhance the wound healing process. Platelets produce and release multiple growth and differentiation factors that are critical for the stimulation and regulation of wound healing,[9] including platelet-derived growth factor (PDGF), transforming growth factor-β (TGF-β), and vascular endothelial growth factor (VEGF).[9] The topical application of PDGF has been shown to accelerate soft tissue healing in experimental wound models.[10-13] The administration of exogenous PDGF has been found to enhance osteogenic differentiation and bone repair in fracture models[14] and critical size calvaria defects.[15] Recent evidence suggests that PDGF may enhance periodontal repair and regeneration.[16] Importantly, PDGF has been shown in an animal model to enhance periodontal regeneration without significant ankylosis or root resorption.[17,18] Cell culture studies further support a significant role for PDGF in the wound healing process by demonstrating its ability to stimulate chemotaxis, cellular activation, and proliferation in fibroblasts and osteoblast-like cells.[19-21]

Given the intricate nature of wound healing, it is apparent that PDGF participates in complex regulatory pathways involving multiple growth and differentiation factors.[20,22] Multiple regulatory peptides have been isolated from bone matrix, including PDGF, insulin-like growth factor-1 (IGF-1), TGF-β, acidic and basic fibroblast growth factor, and bone morphogenetic proteins.[23] Additionally, cell culture studies reveal that the stimulatory effects of PDGF on bone matrix apposition are markedly enhanced by

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the addition of other regulatory peptides, such as IGF-1 and TGF-β.[24] The combination of PDGF and IGF-1 has similarly been shown, in animal models, to enhance the formation of new attachment apparatus[17,25-26] and alveolar bone proximal to endosseous implants.[27] Concerns over the use of purified or recombinant growth factors, particularly bone morphogenic proteins, have included the potential for ankylosis and root resorption.[17,28,29]

Considerable interest has recently emerged over the potential benefits of using platelet-rich plasma (PRP), a highly concentrated form of platelets. Platelet activation results in coagulation and release of regulatory peptides normally sequestered in α granules. Clinically, the resulting platelet gel has been also shown to act as a biologic adhesive and barrier, functioning as a sealant.[30] Autologous platelets have been used clinically primarily for hemostatic control.[31,32] Recently, PRP has been reported to promote hard and soft tissue wound healing.[33-38] For example, PRP has been successfully used in the ophthalmologic treatment of macular holes, which have remained highly recalcitrant to other closure procedures.[37] PRP has also been found to induce rapid bone maturation and increased density in cancellous marrow graft reconstructions of large mandibular continuity defects.[33] Favorable clinical outcomes have been reported following the incorporation of PRP gel in ablative surgical procedures of the maxillofacial region, mandibular reconstruction, repair of alveolar clefts and fistulas, and implant placement.[34,35] Consistent with these clinical reports are in vitro studies demonstrating the capacity of human platelet concentrates to markedly increase the proliferative activity of osteoblast-like cells.[39] Studies in primates further support the importance of platelets in achieving optimal osseous wound repair.[36]

Case report evidence (unpublished data) suggests that PRP may enhance regenerative outcomes using bone allografts, although there is limited clinical and histologic data available on the application of this material. This consecutive case-series report describes the use of PRP in combination with FDBA for alveolar ridge and maxillary sinus GBR procedures. In several patients, core biopsies were obtained as part of implant site preparation, which permitted histological assessment of the maturity of wound healing. The clinical and histologic results are discussed in relation to clinical management, wound healing, and regenerative outcome.

## MATERIALS AND METHODS

Fifteen consecutively treated patients (10 female, 5 male, 25 to 72 years of age) requiring maxillary sinus and/or ridge augmentation for placement of implants participated. Seventeen different areas (14 sinuses, 3 maxillary ridges) were treated using GBR procedures.

Verbal and written informed consent was obtained from each patient prior to treatment. Preoperative hematological assessments included a complete blood count (CBC), with platelet and fibrinogen levels. One week prior to the GBR procedure, 0.12% chlorhexidine gluconate (b.i.d.) was topically applied to the surgical site. Platelet-rich plasma was extracted 1 hour prior to surgery. Approximately 1,000 to 2,500 ml whole blood was obtained using venipuncture and pheresed to obtain 50 to 150 cc of PRP,§ returning red blood cells to the circulation. The PRP was isolated in a 500 ml collection bag containing the anticoagulant citrate. Analysis of the PRP indicated a 3- to 10-fold increase in platelet concentration above presurgical peripheral serum levels. Serum platelet levels were determined using an automated particle counter.‖ Apheresis processing increased the mean platelet count from $244 \times 10^3$ platelets per $mm^3$ (range of $163 \times 10^3$ to $424 \times 10^3$) to $1,163 \times 10^3$ (range of $361 \times 10^3$ to $2,421 \times 10^3$). The largest relative increase in platelet concentration was from $225 \times 10^3$ to $2,421 \times 10^3$ platelets per $mm^3$ following apheresis.

Patients were premedicated with 1 g amoxicillin and nabumetone 1,000 mg immediately prior to the surgery. Surgical sites were disinfected with topical povidone-iodine prior to administration of local anesthesia. Several patients elected the additional use of conscious sedation. Full-partial thickness flaps were elevated at both sinus and ridge augmentation sites. A total of 36 implants were surgically placed in this series. Placement of 29 of the implants was at the time of the GBR procedure in sites where there was sufficient existing bone (≥5 mm) for implant stabilization. All surgeries were performed in a clinical private practice, according to the implant system's¶ standard protocol.

Maxillary sinus grafting was accomplished using the Caldwell-Luc approach.[40-42] Presurgical periapical radiographs were used to approximate the maxillary sinus location and its dimension in an anterior-posterior direction. The composite graft, for all sites, was a mixture of FDBA# and PRP (0.5 gm/2cc PRP). Prior to FDBA/PRP graft placement, the graft was saturated with autologous thrombin-rich extract (Fig. 1). The thrombin-activated graft material was allowed

§ Metronics Sequestra 1000, Denver, CO.
‖ Coulter Counter, Beckman Coulter, Inc., Fullerton, CA.
¶ 3i Implant Innovations, Palm Beach Gardens, FL.
# LifeNet, Virginia Beach, VA.

to gel for several minutes prior to placement in the surgical sites to facilitate its placement. Coagulated PRP gel was used to cover the FDBA/PRP graft. The PRP gel was prepared in 2 steps. First, autogenous thrombin was recovered from a portion of the PRP. Briefly, 100 ml of PRP was pretreated for 6 to 8 minutes with the citrate inhibitor calcium chloride (33 ml), allowed to coagulate, then squeezed to release the platelet-derived thrombin and collected in the serum-rich plasma. Second, the autologous thrombin-rich plasma was mixed with PRP in a 1:4 ratio on a flat surfaced container and allowed to coagulate uncovered for 3 to 5 minutes. The coagulated material was placed onto several dry lint-free gauze pads** which absorbed the excess serum, leaving the formed PRP gel.

Primary closure of the flaps was obtained using either absorbable (polygalactide) or non-absorbable sutures (nylon). Ridge augmentation sites required added flap mobilization and repositioning of the facial mucoperiosteum to permit passive primary closure over the FDBA/PRP. In 2 cases, tenting screws were placed in addition to the FDBA-PRP to facilitate space maintenance. A mattress suturing technique maintained flap closure, with sutures being maintained for up to 3 weeks.

Postoperative protocol included the administration of amoxicillin (500 mg t.i.d. 7 days), along with a nonsteroidal anti-inflammatory agent (nabumetone, 1,000 mg) and dexamethasone (methylprednisolone 4 mg, 7-day dose pack). Patients were seen at 7 to 10 days postsurgery then at 14 to 20 days and every other month until the re-entry procedure.

Re-entry procedures were completed between 120 and 168 days in all but 3 patients. In the latter patients, the second stage procedures were delayed (another 40 to 80 days) due to patient availability. Second stage surgeries were performed approximately 4 to 5 months later, permitting placement of 3 additional implants. A modification of the implant site preparation protocol included the use of a 2 mm trephine in 2 patients, allowing the core material to be submitted for histological evaluation. By assessing bone maturation, the time to abutment connection could be determined based on the healing. In several patients, ostectomy was indicated to place the healing abutment, and the material obtained was also submitted for histological evaluation. Case examples are presented in Figures 2, 3, and 4.

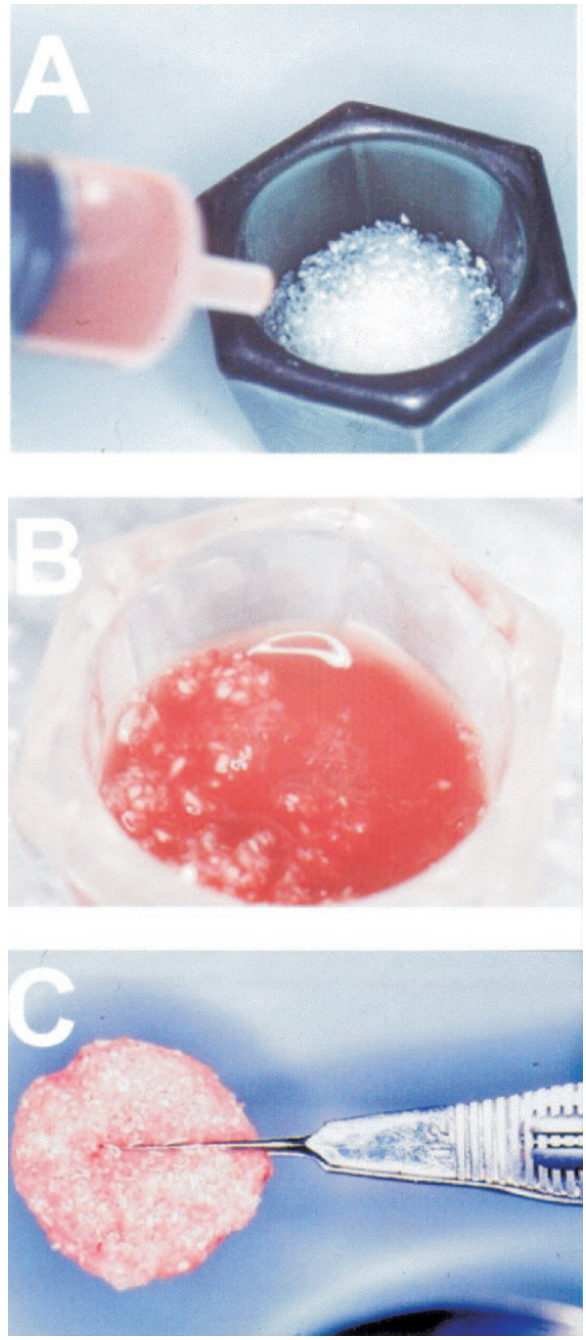


***Figure 1.***
***A.*** *Activated platelet-rich plasma (PRP) is incrementally added to a sterile dish containing FDBA.* ***B.*** *PRP/FDBA coagulated material prior to placement in the surgical site.* ***C.*** *PRP/FDBA coagulated material held by forceps being transferred to surgical site.*

## RESULTS

The mean time between first surgery and re-entry was 154 ± 24.1 (SD) days. Thirty-two of the 36

** Nugauze, Johnson & Johnson, New Brunswick, NJ.

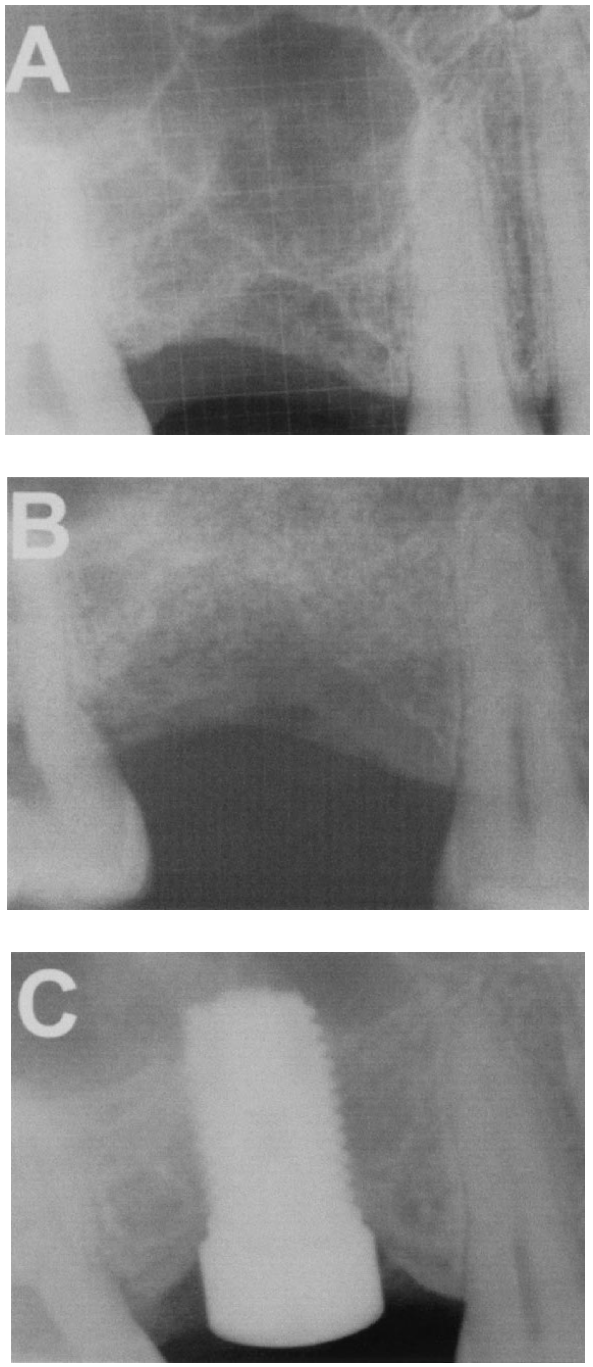


**Figure 2.**
*Case 1.* ***A.*** *Preoperative radiograph illustrates proximity of sinus floor to the crest of the alveolar ridge. Approximately 3 mm of bone separates the crest of the ridge from the sinus floor.* ***B.*** *Postoperative radiograph reveals increased radiopacity at surgical site 4 months after graft placement, with 10 to 13 mm of bone-like material separating crest of ridge from the sinus floor.* ***C.*** *Radiograph of implant at exposure approximately 4 months after insertion of fixture.*

implants (89%) were clinically successful as defined by complete coverage of the entire implant up to the cover screw, the absence of mobility, and radiographic findings consistent with integration (no bone loss or peri-implant radiolucency). The 4 failed implants were clinically loose at the abutment connection stage and were replaced at the second stage surgery with implants that have been subsequently successful.

The histologic specimens confirmed the presence of vital bone formation in close apposition to the residual FDBA particles. No evidence of inflammatory infiltrate or necrosis was observed in any of the specimens. Graft particles generally appeared amalgamated by the bone and, in many instances, extensive areas of osseous bridging and coalescing of graft particles were evident (Fig. 5).

Immediately following PRP procurement, hematological measures were reassessed. Post-treatment platelet counts ranged from 132,000 to 243,000 (mean ± S.E.M. = 188,000 ± 16,900), in contrast to pretreatment counts of 163,000 to 424,000 (mean ± S.E.M. = 245,733 ± 145,600). Hematocrit and hemoglobin levels remained essentially unchanged following treatment.

## DISCUSSION

Autologous PRP has been clinically applied to enhance wound healing in different organ systems[43,44] and to improve the osseous wound healing of autogenous bone grafts in both quality and quantity.[33,45] Anitua compared healing of human extraction sockets with and without PRP and concluded that PRP enhanced and accelerated bone regeneration and soft tissue closure.[38]

Biopsy specimens obtained at 4 to 5 months post-GBR permitted histologic evaluation of the regenerated alveolar ridges. In all 3 cases, new bone formation was demonstrated. FDBA particles were amalgamated with the newly forming bone. Marrow-like tissue formation was observed in 1 histologic specimen. The histologic observations, therefore, suggest that the combination of PRP and FDBA supports the formation of new bone, which is consistent with other clinical and histologic studies using platelet gel[30,33,34] and fibrin glue[46,47] in conjunction with bone grafts. Controlled clinical trials, however, are necessary to determine whether the addition of PRP significantly enhances bone formation and maturation.

Preclinical studies support the concept that platelets possess growth factors that stimulate and enhance the wound healing process, including osseous regeneration.[21,48] Marx et al. have shown a

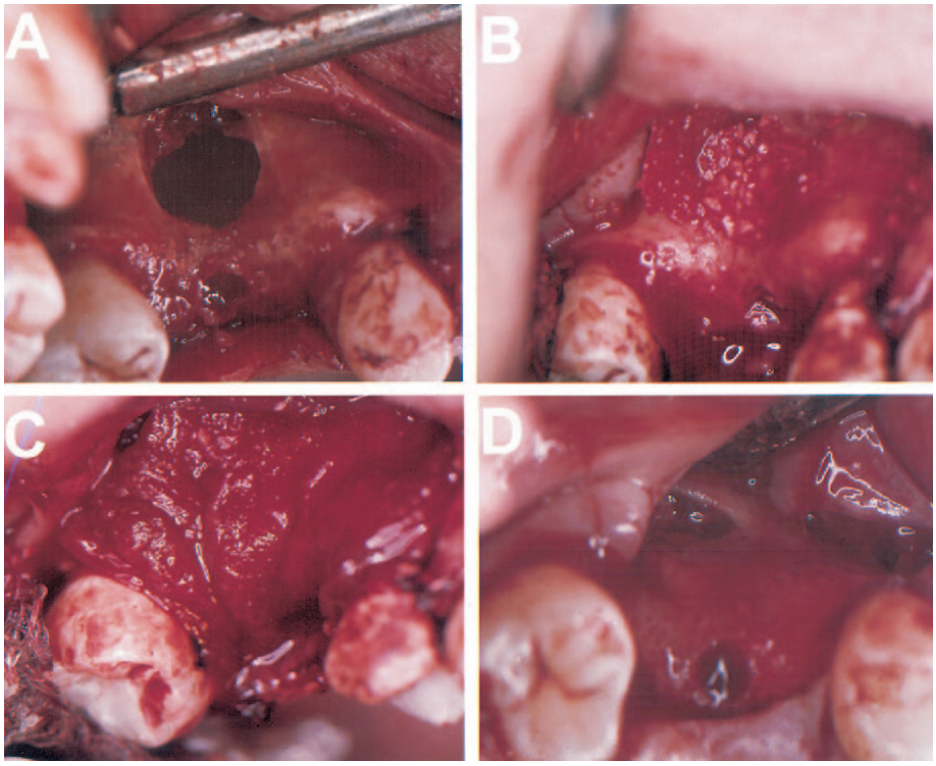


***Figure 3.***
*Case 1. **A.** The sinus cavity is exposed in preparation for PRP/FDBA insertion. **B.** PRP/FDBA is inserted into the sinus cavity. The Schneiderian membrane was thin and tore during maneuvering and a resorbable membrane was placed to isolate the area. **C.** PRP gel was used to cover the window and onlay the buccal and occlusal bone. **D.** Re-entry of graft site at 4 months reveals closure of the surgical window and a significant apical prominence of buccal bone.*

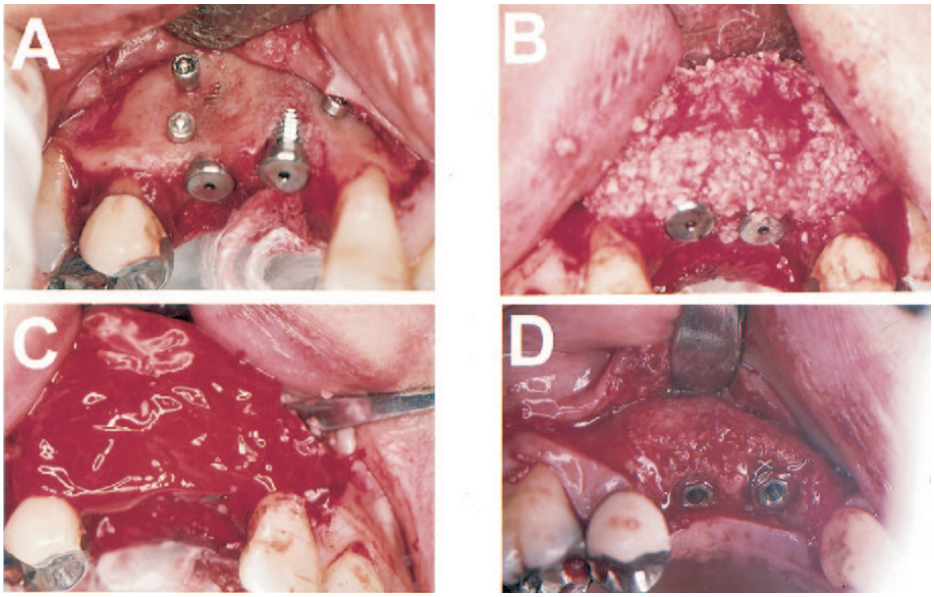


***Figure 4.***
*Case 2. **A.** Implants are shown with exposure of the threads on the facial aspect of the alveolar ridge. **B.** The PRP/FDBA graft exhibits a gel-like consistency and maintains its form, when handled carefully. **C.** A PRP gel was placed to cover the PRP/FDBA graft. **D.** Second-stage surgery exposes implant fixtures, revealing substantial new bone that covers the previously exposed fixtures.*

40% decrease in the healing time of autogenous bone grafts when PRP was incorporated into the site.[33] Their results, together with the current case series, suggest that the use of PRP may allow for earlier implant placement and/or loading.

The use of PRP facilitated the clinical handling of the graft material, which is consistent with previous reports.[30,33,34] Whitman and Berry[30] described a technique using platelet gel for improving the handling of particulate cancellous bone grafts in maxillofacial surgery. Fibrin glue or gel has similarly been used to improve the handling characteristics of graft materials.[46,47]

The clinical procedure for obtaining autologous PRP requires access to specific equipment, including

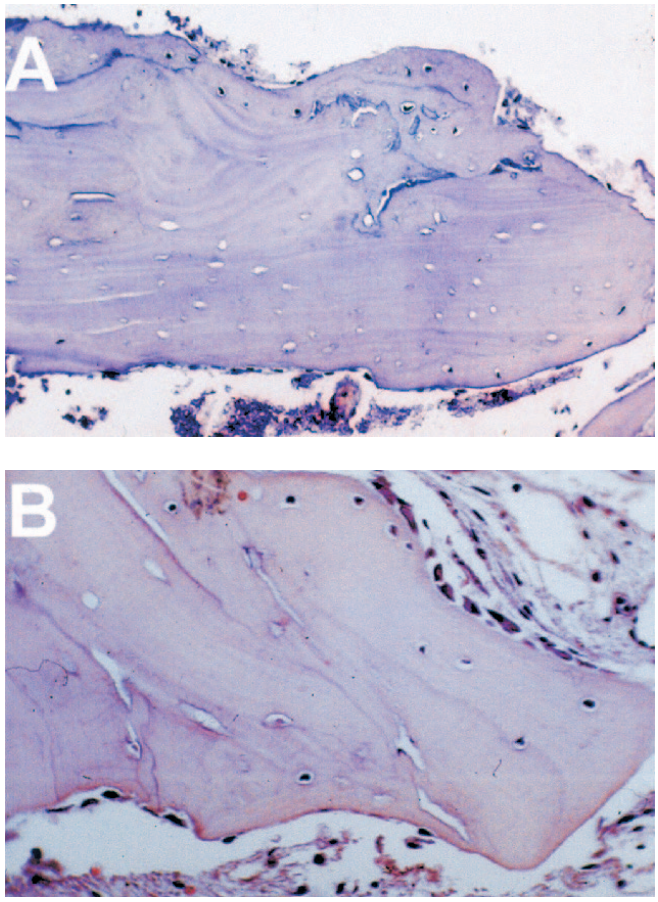


***Figure 5.***
***A.*** *Representative histologic section reveals areas of vital bone and residual graft particles, in the absence of inflammation (original magnification ×10).* ***B.*** *Higher magnification of the same area illustrates vital bone with growth lines surrounding particles of freeze-dried bone allograft (original magnification ×25).*

an ultracentrifuge and gradient density cell separator, either in-office or in a hematology laboratory. To ensure proper procurement and processing, a qualified technician must carry out this procedure. Use of the autologous material within 6 hours of procurement minimizes risk of disease transmission and contamination. Procurement of the PRP results in minimal loss of blood. In these patients, the pheresed material included a workable volume ranging from 60 to 140 cc of PRP, with approximately 10 cc of whole blood left in the infusion setup. Procurement was not associated with any complications. Since a 16-gauge needle is necessary for adequate blow flow, proper access for IV preparation may not be possible in certain patients. Slight increases in hematocrit and hemoglobin levels (2.2% and 5.2%, respectively) were observed in several patients. There was no clinical evidence of clotting time or coagulating time increases, with no observed intraoperative or postoperative bleeding complications. Hematologic measures following platelet apheresis and surgery remained well within normal laboratory ranges.

More recent technologies permit the harvesting of PRP using smaller volumes of blood. A major advantage of increased efficiency in platelet concentration is that sufficient quantities of PRP can be collected, minimizing the need for red blood cell reinfusion and the associated risks. Currently, however, there is little information on what quantities of platelets may be optimal for enhancing osseous regeneration. In certain surgical cases, where limited quantities of PRP are considered necessary, specialized platelet concentrators†† are available for in-office use.

Activation of the PRP in these patients, in contrast to earlier studies, was achieved using autologous thrombin. Bovine thrombin has been used to activate coagulation and precipitate gel formation. The use of bovine thrombin has been associated, however, with the development of antibodies to clotting factors V, XI, and thrombin, with the potential development of life-threatening coagulopathies.[49-52] Multiple reports, for example, have documented the development of bovine thrombin-induced factor V deficiency following exposure to bovine thrombin.[53]

A major advantage of allografts has been the elimination of patient morbidity in graft procurement. However, experimental data suggest that osseous wound repair occurs more slowly following the use of allografts than autogenous bone.[54-56] In an alveolar cleft model, Marx et al. showed complete fill of defects at 6 months with autogenous material, whereas only 30% of the clefts showed viable bone at the same time in areas grafted with the allograft material.[33] Similarly, bone defect models in primates also have shown a general delay in the healing response to freeze-dried bone allografts as compared to autogenous grafts.[57-59] The degree of revascularization of the bone allografts also appears to be slower than with autogenous grafts. Considerable interest, therefore, remains in identifying factors that may improve osseous wound repair following regenerative procedures using allografts.

An added benefit of PRP is its ability to form a biologic gel that may provide graft containment, clot stability, and function as an adhesive. The ability to contain the graft material has been demonstrated to

†† Harvest SmartPrep, Harvest Technologies, Norwell, MA.

be important for regeneration around teeth.[60] An autologous material that possesses a high concentration of biologic mediators may give added benefit to its presence by improving the rate of wound healing and reducing the cost of additional materials.

These clinical and histologic findings suggest that sinus grafting and ridge augmentation with FDBA in combination with PRP provides a viable therapeutic alternative for implant site preparation. The use of allogenic bone replacement grafts, such as FDBA, eliminate the need for surgically harvested autogenous bone. Although the degree of osseous regeneration following the use of FDBA in alveolar and sinus augmentation procedures is generally considered acceptable, the ability to enhance osseous wound healing should improve the quality of regenerative outcome and reduce healing time. Future studies are necessary to determine whether PRP enhances new bone formation or maturation with allogenic bone replacement grafts.

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