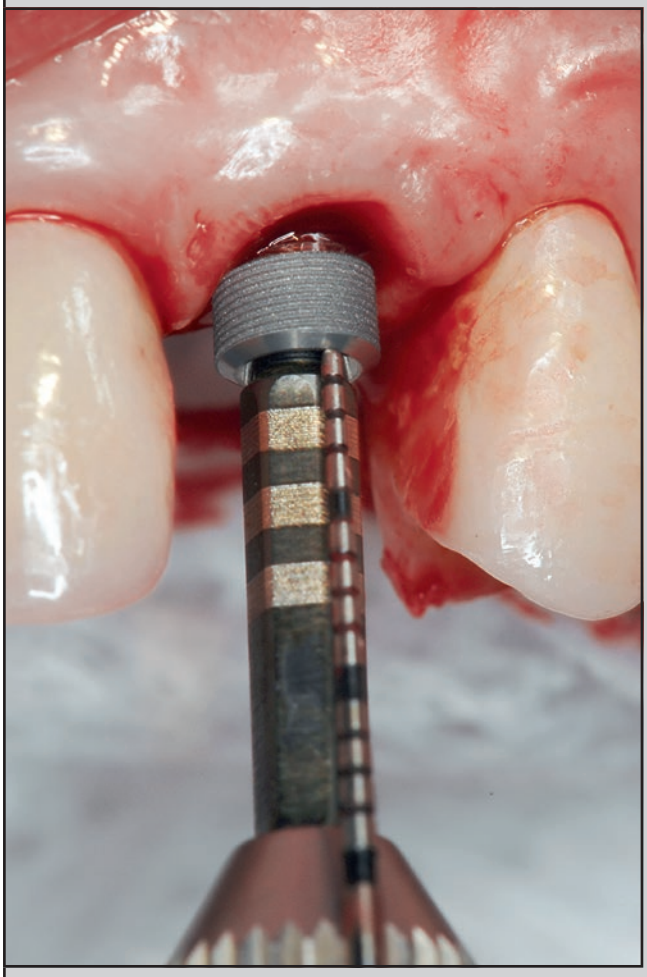
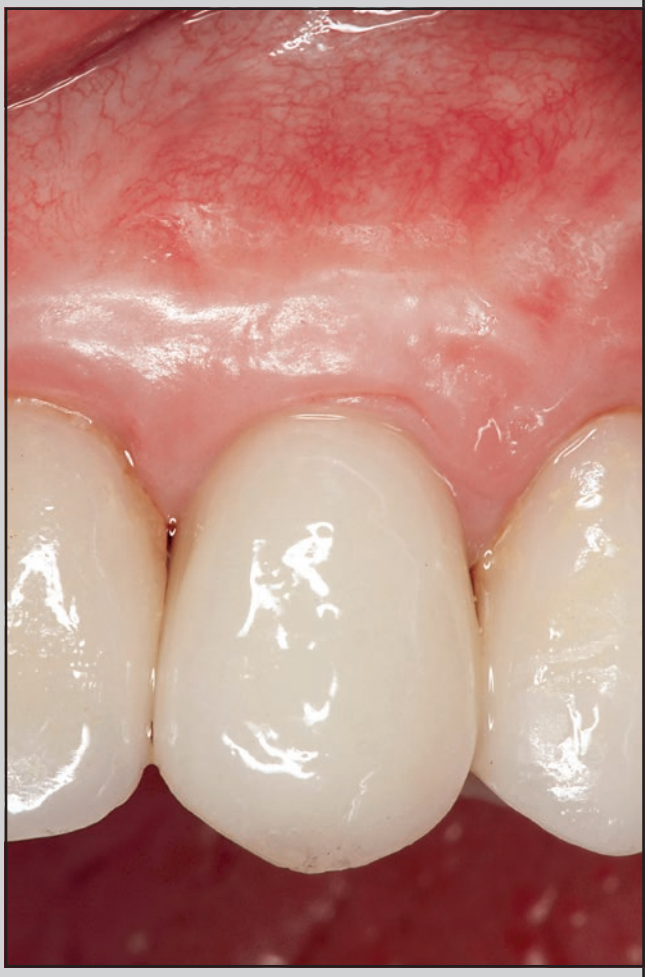
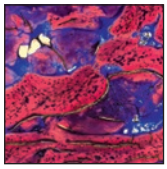




Histologic Evaluation of rhBMP-2 in an Extraction Site Model in the Esthetic Zone: A Series of 16 Cases Preparing for Implant Placement



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Growth factors have been used in numerous oral applications to aid in bone formation after tooth extraction. Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-b superfamily and are involved in the differentiation of pluripotent mesenchymal cells, leading to new bone formation through osteoblastic induction. This study examined histologic wound healing following extraction and ridge preservation using recombinant human BMP-2 (rhBMP-2) and a collagen sponge. Formation of new vital bone was seen, suggesting that this material is a viable option for ridge preservation in preparation for implant placement. Int J Periodontics Restorative Dent 2020;40:171–179. doi: 10.11607/prd.4535

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Adequate alveolar bone determines the practitioner's ability to restore patients' edentulous spaces with dental implants. Often, the alveolar ridge resorbs considerably as it heals and remodels following an extraction, which can restrict the placement of a dental implant as well as compromise the esthetic and functional results.[1,2] Following tooth extraction, significant dimensional changes occur in the buccal-lingual and coronal-apical dimensions, often leaving the center of the alveolar ridge more lingual than the original ridge.[3–5] Schropp et al reported that following single-tooth extraction in humans, the alveolar bone remodeled rapidly.[1] From their clinical measurements, a 50% ridge-width reduction was observed over 12 months, of which two thirds occurred during the first three months of healing; during the first 3 months, an average of 1.2 mm of ridge height was lost.[1] Tan et al[6] reported in a meta-analysis that an extraction without a bone graft can result in a mean height loss of 1.24 mm and mean width reduction of 3.79 mm. Iasella et al, in a nonmolar study, reported up to 4 mm of loss (mean: 29%) in the horizontal dimension within 4 to 6 months after extraction alone.[5]

Various terms have been used in the literature, including ridge preservation, socket preservation, and site preservation. Ridge preservation

was defined in an expert consensus statement from 2009 as "a procedure to minimize vertical and horizontal ridge alterations in postextraction sites."[7] Alveolar ridge preservation has been evaluated in many studies.[8–13] Multiple bone graft materials have been studied for their ability to enhance bone formation in damaged or deficient alveolar ridges,[2,14,15] and to evaluate their bone healing and bone-forming capacity in extraction sockets.[16,17]

Due to the rapid atrophy of the alveolus postextraction, many researchers and clinicians are looking for ways to slow or stop the process by using various techniques and grafting different materials into the sockets.[18] It has been observed that grafting materials helped mitigate and avoid volume reductions and surface invaginations in alveolar ridges.[19] Grafts could also act as a scaffold for new bone formation.[19] Some clinicians and researchers categorize the grafts according to this mode of action,[19] while others classify grafts according to the source from which they are derived.[20] The three general types of bone grafting material are autogenous grafts, allografts, and xenografts.[21] Each type can be used in different clinical situations depending upon the outcome desired.

Certain alveolar ridge preservation procedures utilizing alternative techniques to guided bone regeneration have been pioneered and approved by the Food and Drug Administration for clinical use in extraction sockets. Recombinant technologies utilize the osteoinductive potential of recombinant human bone morphogenetic protein-2 (rhBMP-2) delivered on an absorbable collagen sponge (ACS). rhBMP-2 is manufactured using well-established molecular biology techniques under a tightly controlled process that ensures consistency and sterility of pure solutions of standard BMP-2, a naturally occurring osteoinductive molecule important in healing and regenerating bone.[22]

A systematic review on the outcomes of alveolar ridge preservation with rhBMP-2/ACS concluded that the application of rhBMP-2/ACS in extraction sockets has a dose-dependent positive effect in preserving the alveolar ridge width when compared to placebo; however, it is not shown to prevent alveolar ridge-height loss.[23] Fiorellini et al showed in their randomized, masked, placebo-controlled multicenter clinical study that the novel combination of rhBMP-2 and a commonly utilized collagen sponge had a striking effect on de novo osseous formation in extraction sockets, which allowed the placement of dental implants in the ideal prosthetic location.[24] Clinical evidence in prospective case series demonstrates clinical and radiographic effectiveness of using immediate implant placement combined with rhBMP-2/ACS graft in achieving desired prosthetic outcomes in uncontained nonmolar and molar extraction sites.[25,26]

The objective of this study was to conduct a histologic analysis of rhBMP-2/ACS graft material (Infuse, Medtronic) at 5 months ± 4 weeks postgrafting of maxillary (nonmolar) extraction sockets. The purpose and clinical relevance of this study is to highlight an evidence-based approach to material selection for extraction-site preservation and to provide histologic proof of principle of de novo bone formation following ridge preservation with rhBMP-2/ACS.

Materials and Methods

Study Design

This study is a case series to retrospectively examine the histologic findings of extraction sockets treated with rh-BMP-2/ACS on 16 subjects. The subjects were enrolled, treated, and had histologic samples collected in a previous clinical trial.[27] That study was approved by an institutional review board (IRB) and performed in a private practice setting from March 2009 through January 2011. All subjects provided written informed consent as required by the IRB before participating in that study. This current retrospective histologic analysis was granted an IRB exemption.

Inclusion criteria included provision of informed consent, being 18 years of age or older, and documented patient treatment plans necessitating one or more single implants replacing missing or nonrestorable teeth in the maxilla within the anterior region in tooth sites 14 to 24 (FDI system).

Exclusion criteria included: insufficient interocclusal space for implant placement and restoration at the study site from the previous clinical trial; any tooth adjacent (mesial and/or distal) to the study site that

was ankylosed; greater than 2 mm of vertical bone loss at the study site, as measured from the midbuccal crest of bone on the adjacent teeth; untreated rampant caries and/or uncontrolled periodontal disease; Angle Class II division 2 malocclusion; use of tobacco within last 6 months from date of core biopsy; uncontrolled diabetes (subject history does not reveal the absence of control of diabetes mellitus); current alcohol or drug abuse; systemic or local disease or condition that would compromise postoperative healing and/or osseointegration; use of any substance that will influence bone metabolism; history of radiation in the head and neck region; known pregnancy (in-office pregnancy tests were completed); deemed unlikely to be able to comply with study procedures, according to judgment of investigator(s); and previous enrollment or randomization of treatment in another clinical trial.

A total of 16 subjects were enrolled for histologic sampling. Each participant presented with a single tooth from maxillary first premolar to first premolar with a condition or symptom condemning these teeth to extraction. Complete clinical examinations were carried out, including a full-mouth series of radiographs.

All patients in the previous clinical trial underwent the same surgical procedure. Enrolled subjects received one dose of preoperative antibiotics (at the discretion of the investigator) and 0.12% chlorhexidine rinse (15 mL). Following local anesthesia, teeth were extracted first by using a periotome circumferentially on the tooth. The tooth was luxated with an elevator and removed using appropriate forceps. If luxation was not sufficient, or in the case of multirooted teeth, teeth were sectioned in a mesial/distal dimension using a high-speed handpiece and bur. After extraction, the socket wall was debrided with a surgical curette and irrigated with normal saline. An assessment was then made to ensure that there was not greater than 2 mm of vertical bone loss at the study site, as measured from the midbuccal crest of bone on the adjacent teeth.

Four to eight perforations of the socket wall cortical plates were made using a 1/4 round bur (Brasseler). The XX Small 0.7 cc rhBMP-2–soaked ACS (INFUSE Bone Graft, Medtronic) was cut into strips and placed to fill the defect sites. A larger strip of ACS (INFUSE sponge soaked with BMP as a membrane) was then placed over the entire treatment site. Tension-free soft tissue wound closure was established without primary closure. Postoperative care included analgesics, a 7- to 10-day course of oral antibiotics, and twice daily 0.12% chlorhexidine rinse.

After 5 months of healing and at the time of dental implant insertion, biopsy samples were taken using a 3-mm–diameter (2-mm internal diameter) trephine drill to obtain a core of at least 8 to 10 mm in length, which was placed into formalin solution and shipped to the laboratory for processing. The samples were fixed, decalcified, and embedded in paraffin. The cores were processed by a histologist at the Transport Research Laboratory in Wokingham, United Kingdom. Histologic and histomorphometric analyses were performed at the UT Health School of Dentistry Department of Periodontics to assess the vital bone quality and quantity in treating extraction-site defects with rhBMP.[28–30]

Results

Clinical Findings

All 16 subjects had uneventful healing with minimal swelling and inflammation (Figs 1 to 7). There were no signs of postoperative infection, and no adverse events occurred during the interval between ridge preservation and implant placement. The soft tissue was pink and healthy at reentry, showing no signs of inflammation or infection. Following adequate flap reflection, clinical evidence of bone regeneration was present, which allowed for implant placement in all 16 subjects with subsequent successful immediate provisionalization and final restoration.

Histologic Findings

Sixteen histologic samples were evaluated (Fig 8). Vital bone formation was seen in all samples, with noted signs of vascularity. Histomorphometric analysis determined the percentage of vital bone and percentage of connective tissue. Descriptive statistics, including mean, range, and standard deviation (SD), were calculated for all samples (Table 1). The mean (± SD)

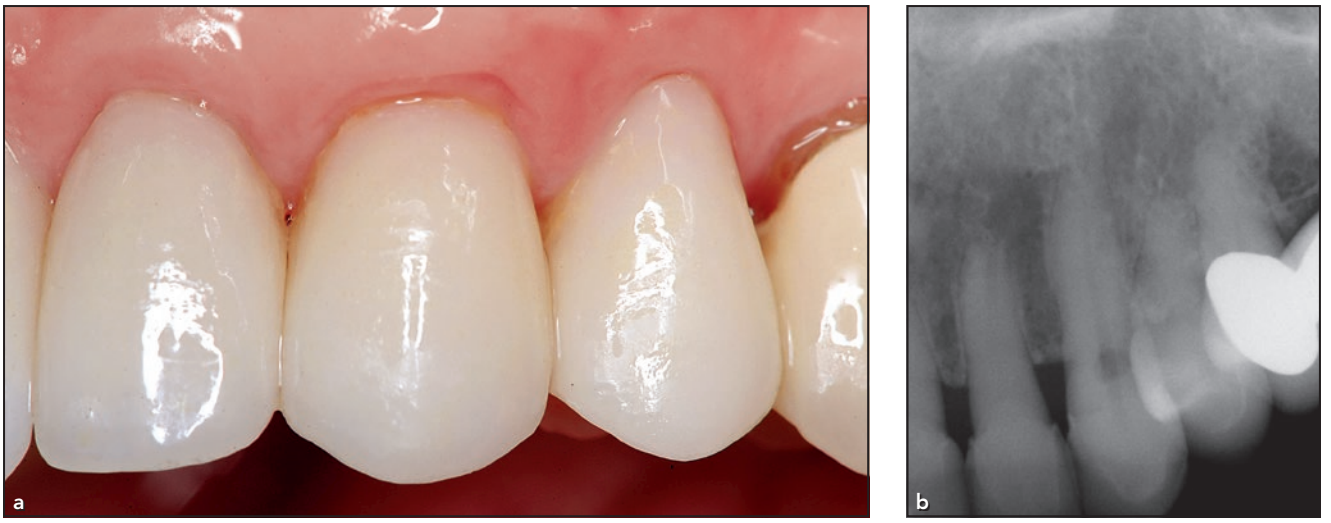


Fig 1 *Preoperative* (a) *clinical view of the restored crown on a maxillary left canine and* (b) *periapical radiograph of the tooth with internal/external resorption.*

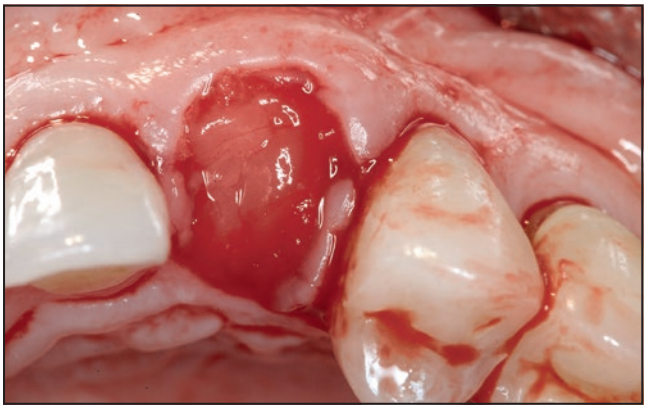
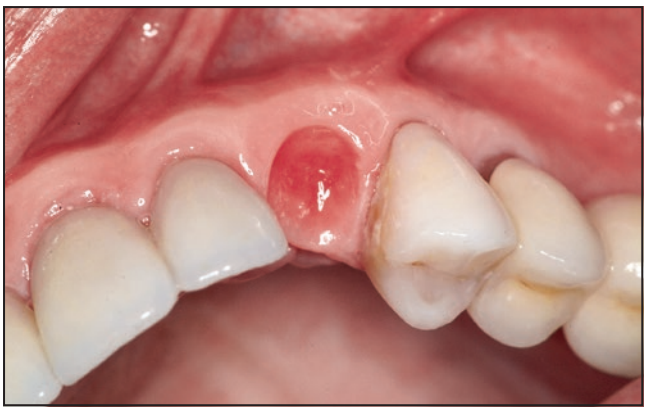


Fig 2 (left) *Infuse sponge soaked with rhBMP-2 and the ACS collagen membrane placed over the treatment site prior to suturing.*

Fig 3 (below left) *Excellent ridge preservation and soft tissue health are seen at 2 months postoperative.*

Fig 4 (below right) *Histologic core collection prior to completion of osteotomy preparation.*



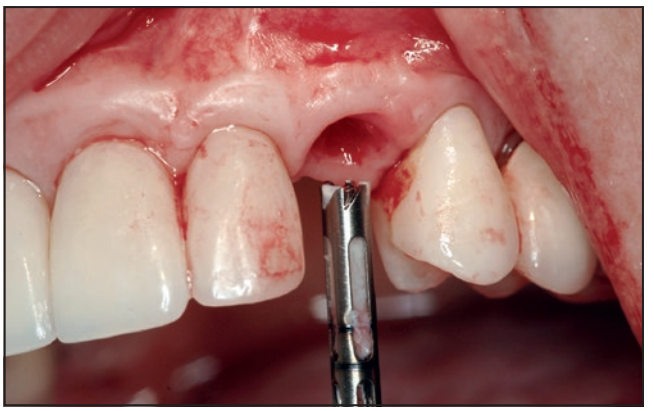
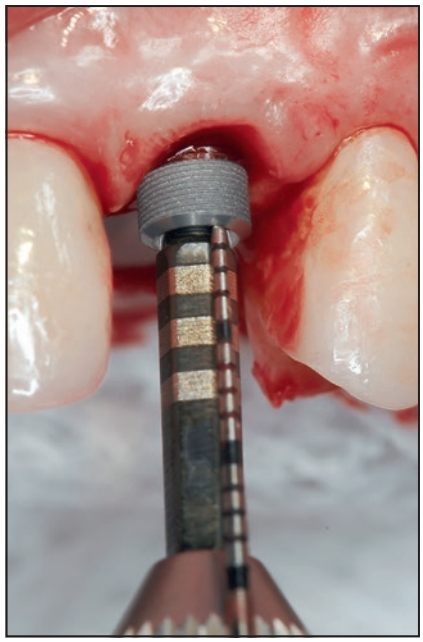
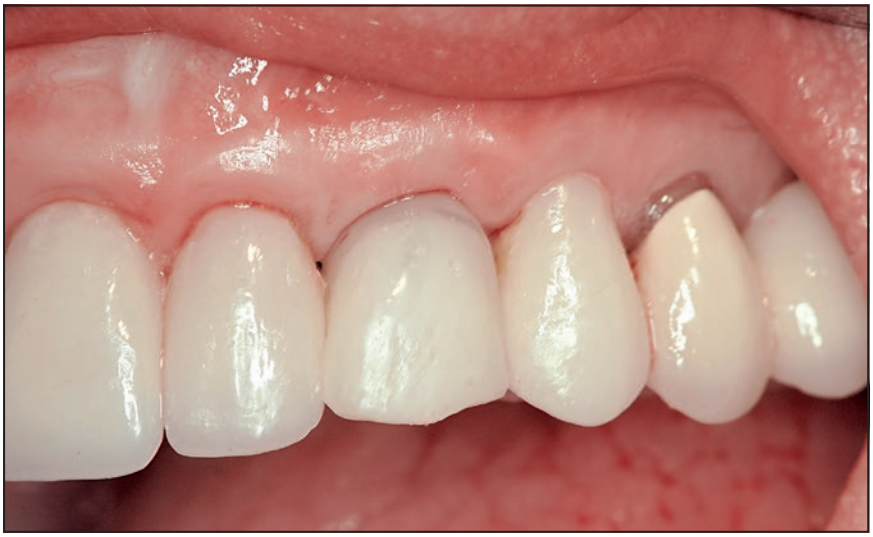


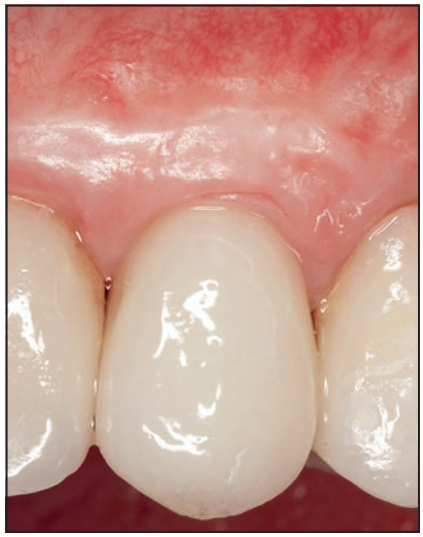
Fig 5 (right) *Implant placement with 35 Ncm and an implant stability quotient of 65 for immediate implant temporization.*

Fig 6 (below left) *Immediate provisional restoration left out of function.*

Fig 7 (below right) *Final restoration, a computer-aided design/computer-assisted manufactured zirconia abutment and an e.max crown, seated at 8 weeks after implant placement.*







percentage of vital bone observed 5 months ± 4 weeks after alveolar ridge preservation with rhBMP-2/ACS was 61.58% ± 14.49%. Mean percentage of connective tissue observed after alveolar ridge preservation with rhBMP-2/ACS was 38.42% ± 14.49% in all 16 histologic samples.

Discussion

In an attempt to minimize postextraction bone resorption and maintain essential crestal bone morphology prior to implant placement, ridge preservation procedures have become standard treatment following tooth removal.[13] A variety of bone grafting materials and membranes have been introduced for ridge preservation. Successful grafting has been accomplished with particulate autogenous, allogeneic, xenogeneic, and synthetic bone grafts and bone-graft substitutes; barrier membranes; and autogenous and allogeneic block grafts

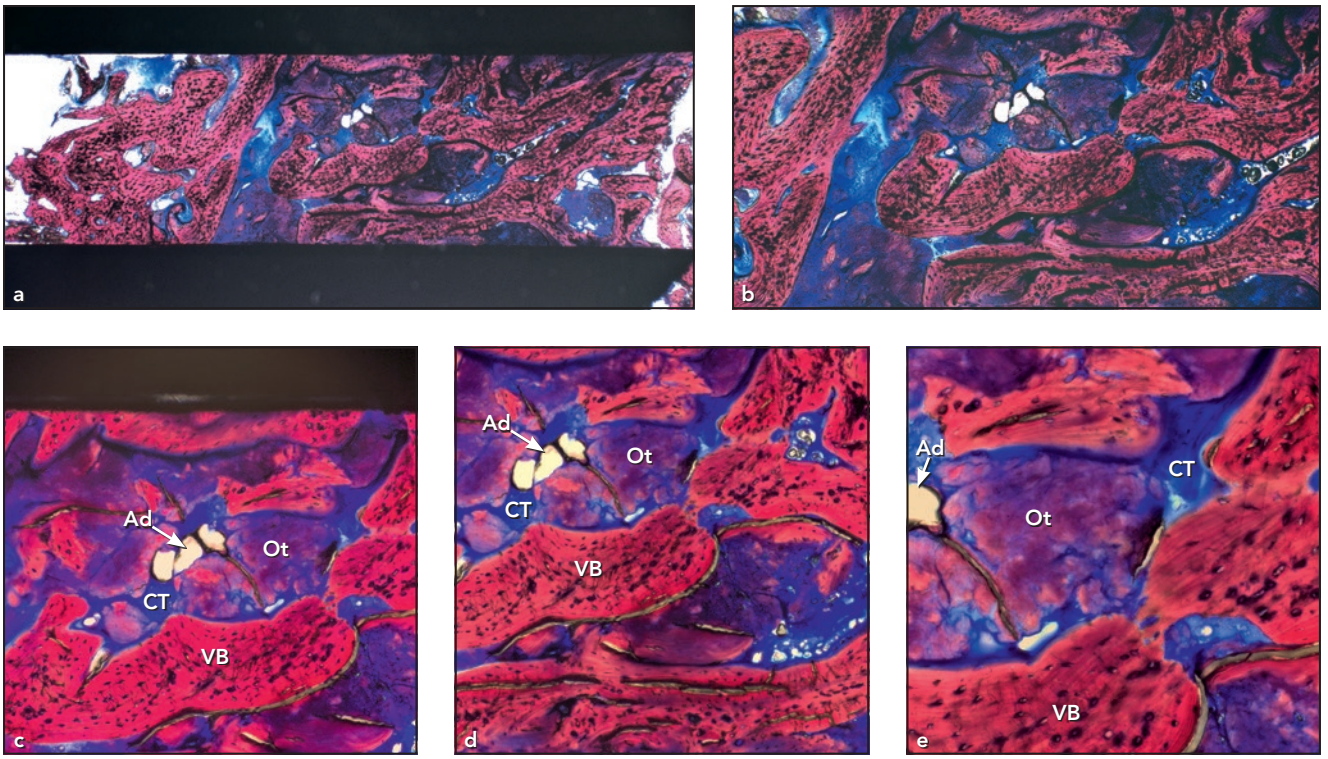


Fig 8 *Histologic sample.* (a) *Excellent vital bone is seen at ×25 magnification.* (b) *Highly active vital bone can be seen at 4 months postextraction (×50 magnification).* (c to e) *The sample (×100 magnification) shows vital bone (VB), osteoids (Ot), connective tissue (CT), and adipose (Ad).*

Table 1 Percentage of Vital Bone and Connective Tissue in Histologic Extraction-Site Bone Core Biopsy Samples

Histologic sample, no.	Vital bone, %	Connective tissue, %
1	66.80	33.20
2	44.70	55.30
3	75.00	25.00
4	69.90	30.10
5	66.30	33.70
6	65.60	34.40
7	76.30	23.70
8	16.20	83.80
9	56.10	43.90
10	69.00	31.00
11	58.60	41.40
12	59.40	40.60
13	70.80	29.20
14	69.10	30.90
15	64.80	35.20
16	56.70	43.30
Max	76.30	83.80
Min	16.20	23.70
Mean ± SD	61.58 ± 14.49	38.42 ± 14.49

SD = standard deviation.
Samples were extraction-site bone core biopsy samples.

and composite grafts. Bone healing and subsequent new bone formation after grafting takes place via osteogenesis, osteoinduction, and/or osteoconduction, dependent upon the type of graft used.[31,32] Osteogenic graft materials supply the viable osteoblasts that form new bone, whereas osteoinductive grafts stimulate pluripotential mesenchymal cells to differentiate into osteoblasts that can form new bone. However, osteoconductive graft materials merely act as a lattice for cell growth, permitting osteoblasts from the wound margins to infiltrate the defect and migrate across the graft.[33] Bone substitutes have gained increasing acceptance as alternatives to autologous bone for patients requiring bone augmentation in an

effort to decrease the cost and morbidity associated with autologous graft harvest. An ideal bone substitute would mediate recruitment of mesenchymal cells derived from the host site and have bioactive effects on ossification (osteoinduction). Furthermore, it would be osteoconductive, providing three-dimensional scaffolds for the ingrowth of vessels and osteoprogenitor cells. Finally, it would be resorbable. Extraction sockets are considered a reliable model for the evaluation of bone healing.[34] Under normal circumstances, undisturbed extraction sockets show evidence of new bone formation within 30 days.[35]

This study examined the effect of rhBMP-2/ACS graft material in nonmolar extraction sockets. Histologic evaluation of bone quality is an essential element when determining the most appropriate grafting material for utilization during ridge preservation procedures. Ideally, the graft material should have a quick turnover, minimizing residual particles after healing and enhancing the formation of vital bone. Bone quality also is an important factor affecting the placement and the functional and esthetic success of dental implants.[36]

The histologic results of vital bone seen in this study (61.58% ± 14.19%) with a reentry time between 4 and 6 months were superior to previous results when compared to allografts, xenografts, and alloplasts. The results of the current study compare favorably and show a higher percentage of vital bone than mineralized FDBA,[28–30] demineralized FDBA,[28,30] or a combination of mineralized and demineralized FDBA.[28] Comparing the present results to xenograft and alloplast studies,[37–40] the rhBMP-2/ACS was superior in vital bone formation compared to deproteinized bovine bone mineral (BioOss, Geistlich Pharma),[41] BioOss Collagen,[15] or BioOss combined with platelet-derived growth factor-BB,[38] magnesium-enriched hydroxyapatite and calcium sulfate,[39] and nanocrystalline hydroxyapatite embedded in a silica gel matrix (Nanobone, Artoss).[40] The results of the current study suggest that use of rhBMPs/ACS may provide a higher percentage of vital bone formation in ridge preservation procedures.

Conclusions

Growth factors have been used in numerous oral applications.[24,26,42,43] The current study examined histologic wound-healing following extraction and ridge preservation using rhBMP-2 on a collagen sponge. Robust formation of new vital bone was seen, suggesting that this material is a viable option for ridge preservation. All patients were able to have immediate provisional and final restorations placed on the dental implants. The human histologic proof of principle validates rhBMP-2 as an excellent material for socket preservation and for the development of ideal tooth-replacement sites. Additional studies are required with a positive control group to scientifically compare rhBMP-2 to alternative biomaterials.

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