Clinical Applications of Recombinant Human Bone Morphogenetic Protein-2 for Bone Augmentation Before Dental Implant Placement

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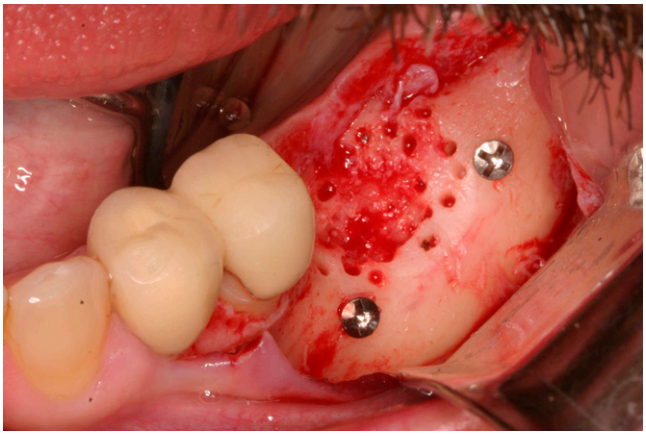

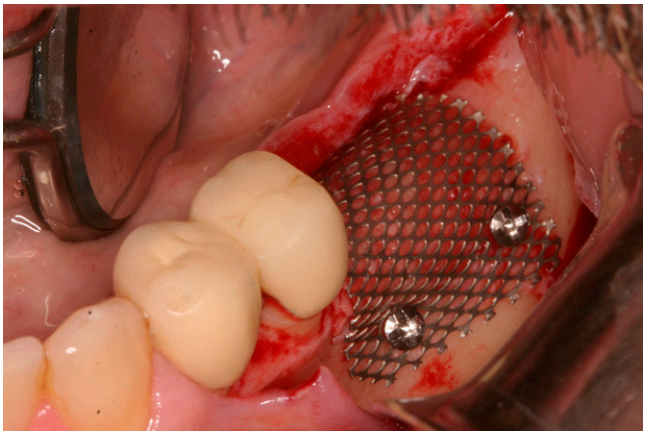

Introduction: Bone morphogenetic proteins (BMPs) are members of the transforming growth factor-β superfamily. They are involved in the differentiation of pluripotent mesenchymal cells, and new bone is formed through osteoblastic induction. Therefore, BMPs are commonly implicated in bone remodeling and regeneration. Recombinant human BMP-2 with absorbable collagen sponge (rhBMP-2/ACS) as its carrier recently received Food and Drug Administration approval for clinical use in sinus augmentations and localized ridge preservation after extractions. This article discusses the clinical use of rhBMP-2/ACS for alveolar ridge repair after extraction and ridge augmentation procedures before dental implant placement.

Case Presentation: Two clinical cases that required socket and ridge augmentation, before dental implant placement, were treated with rhBMP-2/ACS. In socket augmentation, rhBMP-2/ACS and 20% of mineralized cancellous and cortical bone allograft were used. For ridge augmentation, guided bone regeneration using titanium mesh with fixation pins and a mixture of rhBMP-2/ACS and mineralized bone allograft was performed. Clinical and radiographic evaluation of the treated areas after 6 months of healing showed excellent bone regeneration that facilitated subsequent implant placement. In addition, healing of soft tissue at rhBMP-2-grafted sites appeared to be accelerated.

Conclusion: rhBMP-2 can be an agent that is used to promote socket repair as well as ridge augmentation when combined with a small component of mineralized bone allograft. *Clin Adv Periodontics* 2011;1:118-131.

Key Words: Alveolar ridge augmentation; bone morphogenetic protein; dental implants.

Background

In the past decade, the application of recombinant technologies has produced biomimetic devices that stimulate tissue replacement.[1] One example is recombinant human bone morphogenetic protein-2 (rhBMP-2) on an absorbable collagen sponge (ACS) carrier.‡ This commercially available product stimulates host cells to differentiate into bone forming cells.[2] As such, it was recently approved by the Food and Drug Administration (FDA) for clinical use in sinus augmentation and localized alveolar ridge augmentations for defects associated with extraction sockets. In this product, the growth factor is added to an ACS carrier. This article discusses the clinical use of rhBMP-2 for alveolar ridge repair after extraction and ridge augmentation procedures before dental implant placement.

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‡ INFUSE Bone Graft, Medtronic, Memphis, TN.

Extraction Site Defects

Alveolar bone loss after tooth extraction is well documented,[3,4] with significant horizontal bone resorption occurring shortly after tooth removal that approached 50% of the baseline ridge width at 12 months.[5] This bone remodeling is unavoidable because of the loss of the bundle bone,[6] and hence, it adversely impacts the ability to properly place dental implants. This is particularly noteworthy in the esthetic zone because studies[6-9] found that the vast majority of patients present with a thin buccal plate, which undergoes substantial vertical and horizontal crestal bone loss after tooth extraction,[6] thus resulting in a residual ridge that is deficient in width to house a dental implant and also have a minimum of 1.8 to 2 mm of buccal bone thickness needed for long-term stability of the hard- and soft-tissue profiles around the dental implant.[7-9] In addition, it was observed that more severe bone loss occurred in clinical situations in which teeth were extracted as a result of advanced periodontal disease because the inflammatory disease resulted in circumferential vertical and horizontal bone loss. Grunder et al.[10] discussed ideal implant positioning in the esthetic zone and pointed out that the presence of bone determines soft-tissue contour, and that clinicians need to focus on bone volume to achieve ideal esthetic results. There is a generalized agreement that socket preservation techniques are beneficial in minimizing bone volume loss after extraction; unfortunately, there is a lack of consensus on the ideal graft materials and techniques to use.[11,12]

Conventional approaches to socket bone grafting for future implant placement involve the use of various graft materials with or without barrier membranes. When the socket walls are intact, osteoconductive graft materials can be used and barrier membranes may not be necessary. However, when socket walls are missing, regenerative techniques that have greater biologic capacity for bone formation are often used. These may include osteoinductive graft materials with or without the use of barrier membranes. Choices of osteoinductive graft materials include autogenous bone, demineralized freeze-dried bone allograft (DFDBA), and rhBMP-2/ACS. Autogenous bone grafts usually require a secondary donor site and are associated with increased morbidity. DFDBA contains miniscule quantities of BMP and is therefore only weakly osteoinductive.[13,14]

TABLE 1 Benefits of Using rhBMP-2 for Socket Augmentation

Promotes soft-tissue healing
Requires no primary wound closure
Minimizes surgery time
Reduces potential postsurgical infection
Accelerates cell migration
Promotes early bone formation

On the contrary, rhBMP-2 is highly osteoinductive and has been evaluated in the socket defect application.[15] Table 1 lists the benefits of using rhBMP-2 for socket augmentation. Table 2 shows research published on using rhBMP-2 for socket repair.

Case Report: Socket Repair

The patient is a 37-year-old female with a history of oral trauma, endodontic treatments, and chronic infections associated with three maxillary anterior teeth (#7 through #9) (Fig. 1a). The three teeth were planned for extraction and socket augmentation. Periapical radiographs and a cone beam computed tomography (CBCT) scan of the maxilla were obtained preoperatively (Figs. 1b and 1c). The CBCT scan showed significant loss of the facial cortex around all three anterior teeth. Before surgery, written informed consent was obtained, and the patient received a loading dose of 1 g amoxicillin, 8 mg dexamethasone, and 10 mL of 0.12% chlorhexidine rinse. After local anesthesia, the incisors #7 through #9 were extracted, and the sockets were thoroughly curetted of all soft tissue remnants (Fig. 1d). The facial cortex was found to be completely absent to the apical regions of the sockets. A bone graft kit,§ which had a 1 × 2-inch ACS and 1.4 cc rhBMP-2 (1.5 mg/mL),‖ was used for the defect repair. The ACS was evenly saturated with rhBMP-2, and 15 minutes were allowed for the binding of rhBMP-2 to ACS before it was cut into smaller pieces and mixed with a small quantity (20% by volume) of mineralized cortical/cancellous bone allograft.¶ The graft mixture was placed into the extraction sockets planned for implant placement (#7 and #9) and gently compressed to fill the socket level with the palatal bone margins (Figs. 1e and 1f). The center socket (#8) planned for the implant bridge pontic was filled with a relatively non-resorbable bovine hydroxyapatite# so that the bone width could be indefinitely maintained. A piece of the rhBMP-2/ACS alone (no bone allograft) was then placed over the sockets to the level of the surrounding gingiva. The collagen sponges were secured using 4-0 chromic gut interrupted sutures in a cross pattern over the sockets. A fixed resin bridge (#6 through #10) was fabricated as a provisional restoration during healing, and acrylic was added to create ovate pontics (Fig. 1g). Periapical radiographs were obtained of the grafted site. The patient was placed on a postsurgical regimen that consisted of a tapering dose of dexamethasone for 2 days (4.5 to 1.5 mg), antibiotic therapy (amoxicillin at 500 mg three times per day for 7 days), 0.12% chlorhexidine rinse twice per day for 2 weeks, and a narcotic analgesic when necessary. At the 2-week postsurgery evaluation, the patient experienced moderate swelling of the upper lip and face but healed without complications. The grafted site was allowed to heal for 5 months. A CBCT

§ XS INFUSE Bone Graft kit, Medtronic.
‖ INFUSE Bone Graft, Medtronic.
¶ MinerOss, BioHorizons, Birmingham, AL.
# Bio-Oss, Osteohealth, Shirley, NY.

TABLE 2 rhBMP-2 and Extraction Socket Augmentation

Reference	Study Design	Sample Size	Location	Agent and Dosing	Study Groups	Assessment Periods	Findings	Conclusion
Matin et al., 2001[35]	Animal model, split-mouth design	60 rats	Mesial root of maxillary first molars	40 μg/100 μL rhBMP-2 with PLGA/GS	2 groups: ■ rhBMP-2/PLGA/GS (test) ■ PLGA/GS only (control)	Animals sacrificed at 3, 5, 7, 14, 21, 28, 56, and 84 days	■ Test group showed slight swelling from days 14 to 28 ■ New bone formation at day 28 for test sites and day 56 for control sites	rhBMP-2/ACS promoted faster and greater new bone formation
Howell et al., 1997[19]	Clinical trial	6 of 12 patients	Maxillary teeth excluding molars	0.43 mg/mL rhBMP-2/ACS	1 group: ■ rhBMP-2/ACS	4 months	■ Mean height response was 0.32 mm (range, −0.94 to 1.57 mm) ■ Mean density response was 248.25 mg/mL (range, 86.06 to 410.44 mg/mL)	0.43 mg/mL rhBMP-2/ACS might not be sufficient for bone induction, but it was safe and technically feasible to use
Cochran et al., 2000[20]	Clinical trial	6 of 12 patients	Maxillary teeth excluding molars with ≥50% buccal bone loss	0.43 mg/mL rhBMP-2/ACS	1 group: ■ rhBMP-2/ACS	■ Implant placement 16 to 30 weeks after extraction ■ Follow-up: 36 months	■ Pain and erythema in 58% of patients between 4 and 24 months after procedure ■ Facio-lingual socket fill was 4.9 ± 2.4 mm ■ Mesio-distal socket fill was 3.7 ± 2.1 mm ■ Fill of socket depth was 10.4 ± 6.6 mm	0.43 mg/mL rhBMP-2/ACS was effective in maintaining ridge width by 4.9 ± 2.4 mm

TABLE 2 (Continued) rhBMP-2 and Extraction Socket Augmentation

Reference	Study Design	Sample Size	Location	Agent and Dosing	Study Groups	Assessment Periods	Findings	Conclusion
Fiorellini et al., 2005[15]	Multicenter RCT	80 patients, 95 defects	Maxillary teeth excluding molars with ≥50% buccal bone loss	0.75 and 1.5 mg/mL rhBMP-2/ACS	4 groups: ■ 0.75 mg/mL rhBMP-2/ACS ■ 1.50 mg/mL rhBMP-2/ACS ■ ACS only (positive control) ■ No treatment (negative control)	4 months	■ Significant increase in bone width in 1.50 mg/mL rhBMP-2/ACS group compared to the other 3 groups ■ Greater number of oral edema and erythema in the rhBMP-2/ACS groups	1.50 mg/mL rhBMP-2/ACS was more effective in preserving ridge width after tooth extraction
Misch, 2010[21]	Case series	10 patients	Failed endodontically treated maxillary central incisors with >50% buccal bone loss	1.5mg/mL rhBMP-2/ACS and mineralized cortical/cancellous bone allograft	1 group: ■ rhBMP-2/ACS and allograft	Reentry at 5 to 6 months	■ 40% had moderate swelling of upper lip and face ■ Changes in ridge width ranged from +0.63 to −2.18 mm ■ Average volume change was −1.07 mm ■ Mean bone quality was D3	Use of rhBMP-2/ACS was effective in preserving ridge width after tooth extraction

Key words used in the PubMed literature search were: rhBMP-2, socket, and extraction socket augmentation. PLGA/GS = polylactic acid and polyglycolic acid copolymer-coated gelatin sponge; RCT = randomized clinical trial.

scan was obtained before implant surgery to evaluate the graft healing and select the appropriate size implants (Fig. 1h). The CBCT scan found favorable regeneration of the alveolar bone and adequate bone volume for implant placement. Clinically, the surgical site presented with adequate hard- and soft-tissue dimensions (Fig. 1i). Under local anesthesia, an incision was made along the ridge crest, and a full thickness mucoperiosteal flap was elevated to expose the residual ridge. Favorable bone fill and regeneration of the facial bone was observed. The implant osteotomies were prepared according to the drilling sequence of the manufacturer, and the bone density was found to be type 3.[16] Two dental implants** were placed in a two-stage surgical approach (Figs. 1j through 1l), and a 4-month healing period was allowed before the implants were uncovered and restored.

Ridge Augmentation

Several procedures, such as onlay bone grafting, ridge splitting, guided bone regeneration (GBR), and distraction

** Osseospeed TX, Astra Tech, Mölndal, Sweden.

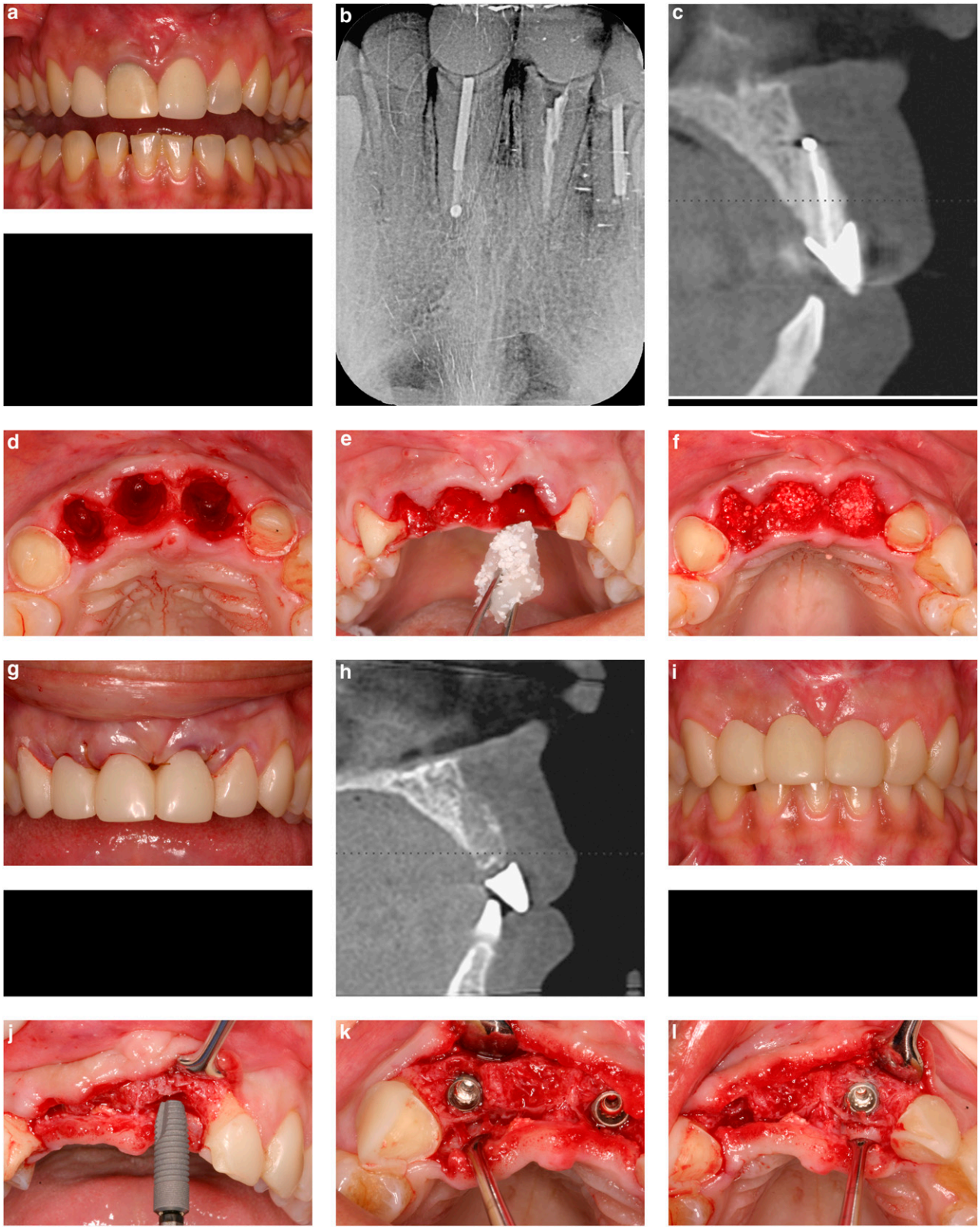

FIGURE 1 Case 1. **1a** Preoperative view of failing maxillary anterior teeth (#7 through #9). The patient had chronic fistulas over the apical mucosa. **1b** A periapical radiograph of the failed maxillary incisors. **1c** A cross-sectional view of a maxillary CT scan revealed no facial bone over the roots. **1d** The maxillary extraction sockets with a lack of a facial cortex. **1e** The rhBMP-2/ACS mixed with bone substitute was placed into the sockets. **1f** The graft mixture was packed level with the palatal bone margins. **1g** A provisional bridge was used as temporary tooth replacement during healing. **1h** A cross-sectional view of a CT scan after 5 months of graft healing. **1i** A preoperative view before implant surgery. **1j** Placement of two implants (Osseospeed TX, Astra Tech) in the reconstructed maxilla. **1k** An occlusal view of the left lateral incisor implant. Note the regeneration of the facial cortex. **1l** An occlusal view of the right central incisor implant. Note the regeneration of the facial cortex.

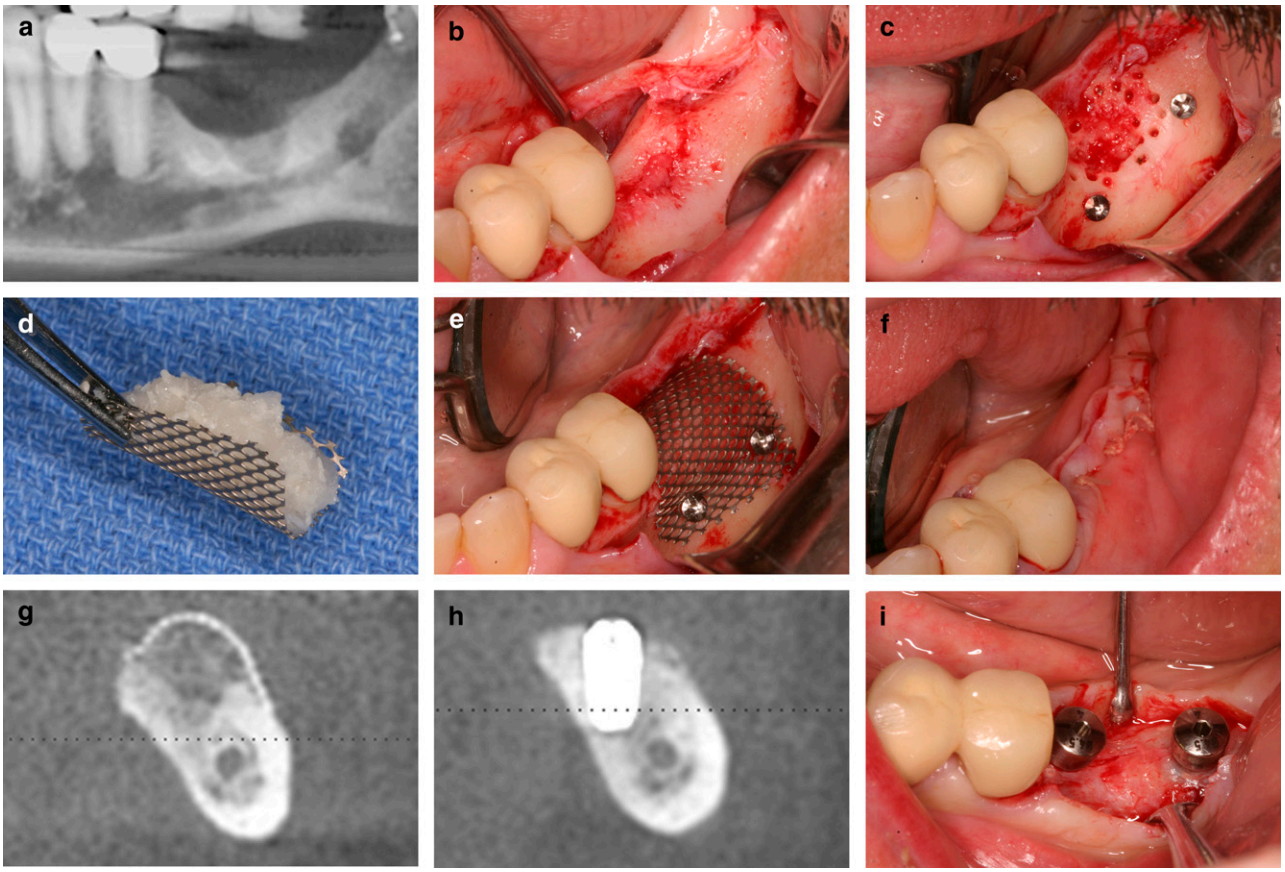

FIGURE 2 Case 2. **2a** A preoperative radiograph of the left posterior mandible revealed a vertical bone defect. **2b** A mucoperiosteal flap was reflected to expose the defect. **2c** The cortex over the defect site was perforated to allow access to the intramedullary stem cells. **2d** The titanium mesh was contoured over the defect and filled with the mixture of rhBMP-2/ACS and mineralized bone allograft. **2e** The titanium mesh was fixated with monocortical screws. **2f** Tension-free primary closure of the flaps over the graft site. **2g** A cross-sectional view of the CT scan of the mandible revealed the regenerated bone under the titanium mesh. **2h** A cross-sectional view of the CT scan after implant placement. **2i** Exposure of the implants for placement of healing abutments after 2 months of healing.

osteogenesis, are available to augment an atrophic residual ridge for implant placement. When significant defects are encountered, autogenous bone graft is often used alone or in combination with other bone substitutes to regenerate larger volumes of bone. The biologic properties of autogenous bone, including properties of osteogenesis, osteoinduction, and osteoconduction, are advantageous in the reconstruction of a severely atrophic ridge. Currently, investigations to determine the feasibility of replacing autogenous bone graft in ridge augmentation with rhBMP-2/ACS are being conducted. Therefore, the use of rhBMP-2/ACS for residual ridge augmentation in this case report is considered an off-label application by the FDA.

Case Report: Ridge Augmentation

The patient is a 42-year-old male with mandibular left partial edentulism and a severe vertical defect. A CBCT scan of the mandible was obtained preoperatively (Fig. 2a). There was ≈4.0 mm of bone superior to the mandibular canal. The original plan was to harvest autogenous bone for the reconstruction of the defect. As an alternative, the use of rhBMP-2 was proposed, and written informed consent for use of the product in an off-label manner was obtained. The patient received a loading dose of 1 g amoxicillin, 8 mg dexamethasone, and 10 mL of 0.12% chlorhexidine rinse. Local anesthesia was obtained using a mandibular nerve block with 0.25% bupivacaine, 1:200,000 epinephrine, and buccal infiltration with 2% lidocaine, 1:100,000 epinephrine. The rhBMP-2/ACS was prepared just before surgery to allow adequate time for protein binding. A bone graft kit[††] was used. A 1 × 2-inch collagen sponge was evenly saturated with the reconstituted rhBMP-2 (1.5 mg/mL) for 15 minutes. It was subsequently cut into smaller pieces and mixed with a small quantity (20% by volume) of mineralized bone allograft.[‡‡]

An incision was made along the ridge crest through keratinized gingiva in the posterior mandible. A lateral releasing incision was made at the base of the retromolar pad. A short anterior releasing incision was made mesial to the most posterior tooth bordering the defect. A mucoperiosteal flap was reflected to completely expose the atrophic ridge (Fig. 2b). The lingual reflection extended to the mylohyoid ridge. The future implant sites were planned, and the size of the mesh needed for graft coverage was assessed. The 0.2-mm-thick titanium mesh was trimmed to extend well posterior to the distal implant site. The lateral borders of the mesh extended slightly beyond the desired area of augmentation to

[††] XS INFUSE Bone Graft kit, Medtronic.
[‡‡] MinerOss, BioHorizons.

TABLE 3 rhBMP-2 and Vertical Ridge Augmentation

Reference	Study Design	Sample Size	Location	Agent and Dosing	Study Groups	Assessment Periods	Findings	Conclusion
Wikesjö et al., 2002[36]	Animal model, split-mouth design	6 dogs	Bilateral posterior mandible	0.40 and 0.75 mg/mL rhBMP-2/αBSM	3 groups: ■ 0.4 mg/mL rhBMP-2/αBSM ■ 0.75 mg/mL rhBMP-2/αBSM ■ αBSM only (control)	Animals sacrificed at 16 weeks	Mean vertical bone augmentation at sites with: ■ 0.4 mg/mL rhBMP-2: 4.9 ± 1.0 mm ■ 0.75 mg/mL rhBMP-2: 5.3 ± 0.3 mm ■ no rhBMP-2: 0.4 ± 0.4 mm	rhBMP-2/αBSM could be a viable alternative to promote vertical ridge augmentation and implant osseointegration
Wikesjö et al., 2003[37]	Animal model, split-mouth design	4 dogs	5 mm critical sized, supra-alveolar, peri-implant vertical defects created in bilateral mandibular premolar region	0.2 and 1.43 mg/mL rhBMP-2/ACS	2 groups: ■ 0.2 mg/mL rhBMP-2/ACS ■ 1.43 mg/mL rhBMP-2/ACS and ePTFE membrane	Animals sacrificed at 8 weeks	■ rhBMP-2/ACS with ePTFE membrane had new bone formation conforming to the ePTFE device ■ Sites without the ePTFE membrane had irregular bone formation that lacked conformity to the implants ■ Mean vertical bone gain at sites with rhBMP-2/ACS and ePTFE: 4.7 ± 0.2 mm; rhBMP-2/ACS only: 3.5 ± 0.9 mm ■ Significantly higher BIC at surface etched implants compared to turned implants in the groups with ePTFE	ePTFE defined the geometry of bone formation in rhBMP-2/ACS induced vertical alveolar ridge augmentation
Wikesjö et al., 2004[38]	Animal model, split-mouth design	4 dogs	5 mm critical sized, supra-alveolar, peri-implant vertical defects created in bilateral mandibular premolar region	4 mg/mL rhBMP-2/ACS	2 groups: ■ rhBMP-2/ACS and ePTFE membrane (test) ■ ACS only and ePTFE membrane (control)	Animals sacrificed at 8 weeks	■ Test sites exhibited erythema and moderate swelling which subsided in 4 weeks ■ Mean vertical bone gain in test sites at turned implants: 4.7 ± 0.3 mm (96% of defect height);	GBR with ePTFE membrane was significantly enhanced with the use of rhBMP-2/ACS

TABLE 3 (Continued) rhBMP-2 and Vertical Ridge Augmentation

Reference	Study Design	Sample Size	Location	Agent and Dosing	Study Groups	Assessment Periods	Findings	Conclusion
							surface etched implants: 4.8 ± 0.1 mm (98% of defect height) ■ Mean vertical bone gain in control sites at turned implants: 1.8 ± 2.0 mm (37% of defect height); surface etched implants: 1.3 ± 1.3 mm (26% of defect height)	
Shimazu et al., 2006[39]	Animal model, split-mouth design	90 rats	Bilateral posterior mandible	1 μg/mm^3 rhBMP-2/PLGA/GS	3 groups: ■ rhBMP-2/PLGA/GS (test) ■ PLGA/GS only (positive control) ■ No treatment (negative control)	Animals sacrificed at 1, 2, 4, 8, and 12 weeks	■ New bone formation started in the first week, by 8 weeks PLGA/GS was resorbed, and by 12 weeks regenerated and native bone integrated ■ Control groups had limited or no new bone formation	Height and volume of new bone formation peaked at 4 weeks and was maintained until 12 weeks
Wikesjö et al., 2008[40]	Animal model, split-mouth design	12 dogs	5 mm critical sized, supra-alveolar, peri-implant vertical defects created in bilateral mandibular premolar region	0.75, 1.5, and 3.0 mg/mL rhBMP-2	4 groups, implants* coated with: ■ 0.75 mg/mL rhBMP-2 (test 1) ■ 1.5 mg/mL rhBMP-2 (test 2) ■ 3.0 mg/mL rhBMP-2 (test 3) ■ Uncoated (control)	Animals sacrificed at 8 weeks	■ Significant swelling associated with the test groups ■ Significant vertical bone gain in test group 1: 4.4 ± 0.4 mm; test group 2: 4.2 ± 0.7 mm; test group 3: 4.2 ± 1.2 mm versus control group: 0.8 ± 0.3 mm ■ Control group had significantly higher BIC compared to test groups (79% versus 30% to 39%)	rhBMP-2-coated implants appeared to induce vertical bone augmentation in peri-implant defects

TABLE 3 (Continued) rhBMP-2 and Vertical Ridge Augmentation

Reference	Study Design	Sample Size	Location	Agent and Dosing	Study Groups	Assessment Periods	Findings	Conclusion
Freilich et al., 2008[41]	Animal model	20 mice	Calvarium	20 μg ng/ rhBMP-2	4 groups: ■ Ti only (negative control) ■ Ti and rhBMP-2 (test) ■ HA-coated Ti (positive control) ■ HA-coated Ti and rhBMP-2 (test)	Animals sacrificed at 21 days after procedure	New bone formation seen in test sites only	ng/rhBMP-2 was effective in promoting new vertical bone formation
Kawakatsu et al., 2008[42]	Animal model, split-mouth design	6 dogs	6 mm high × 30 mm long × 8 mm wide defects were surgically created in bilateral posterior mandible regions	0.4 mg/mL rhBMP-2/PLGA/GS	2 groups: ■ rhBMP-2/PLGA/GS (test) ■ PLGA/GS only (control)	Animals sacrificed at 16 weeks after surgery	■ Post-surgical swelling in test sites for the first 2 weeks after surgery ■ Significantly greater new bone formation in test sites: 4.3 ± 0.9 mm; control sites: 0.22 ± 0.28 mm ■ Significantly greater total bone mineral content in test sites: 133 ± 33 mg/mm; control sites: 80 ± 19 mg/mm	rhBMP-2/PLGA/GS might promote significant bone formation and provide space for new bone formation
Kim et al., 2010[43]	Animal model, split-mouth design	15 rabbits	Calvarium	0.05 mg/mL rhBMP-2	3 groups: ■ Collagen block† and mineralized bone allograft block‡ infused with rhBMP-2 (test) ■ Collagen block§ and mineralized bone allograft block‖ with PTFE membrane (test)	Animals sacrificed at 12 weeks	■ Mean vertical bone height gained with collagen block** with rhBMP-2: 1.89 ± 0.55 mm; mineralized bone allograft block†† with rhBMP-2: 4.11 ± 0.41 mm ($P < 0.05$) ■ Mean area of new bone fill with collagen block‡‡ with rhBMP-2: 16.61 ± 6.13%; mineralized bone allograft block§§	Vertical bone augmentation was not enhanced by the application of rhBMP-2

TABLE 3 (Continued) rhBMP-2 and Vertical Ridge Augmentation

Reference	Study Design	Sample Size	Location	Agent and Dosing	Study Groups	Assessment Periods	Findings	Conclusion
					■ Collagen block[¶] and mineralized bone allograft block[#] only (control)		with rhBMP-2: 30.85 ± 7.45% ($P < 0.05$) ■ NSSD between blocks with rhBMP-2 and blocks with membranes	

Key words used in the PubMed literature search were: rhBMP-2, vertical bone augmentation, and vertical ridge augmentation. PTFE = polytetrafluoroethylene; ePTFE = expanded polytetrafluoroethylene; BIC = bone-to-implant contact; HA = hydroxyapatite; ng/rhBMP-2 = non-glycosylated recombinant human bone morphogenetic protein-2; Ti = titanium; αBSM = calcium phosphate cement carrier; PLGA/GS = polylactic acid and polyglycolic acid copolymer-coated gelatin sponge; NSSD = no statistically significant difference.

* Nobel Biocare, Zurich, Switzerland.
† Bio-Oss, Osteohealth.
‡ Puros, Zimmer Dental, Carlsbad, CA.
§ Bio-Oss, Osteohealth.
‖ Puros, Zimmer Dental.
¶ Bio-Oss, Osteohealth.
# Puros, Zimmer Dental.
** Bio-Oss, Osteohealth.
†† Puros, Zimmer Dental.
‡‡ Bio-Oss, Osteohealth.
§§ Puros, Zimmer Dental.

contact the residual ridge. The mesh was molded into a U-shape and fitted onto the atrophic mandible with a periosteal elevator. The cortex of the mandibular crest was generously perforated to produce bleeding in multiple sites with a #6 round carbide bur. The pilot holes for the fixation screws were also prepared at this time (Fig. 2c). The concave portion of the mesh was packed with the rhBMP-2/ACS and allograft mixture (Fig. 2d), reinserted over the mandible, and compressed into place. Two monocortical fixation screws (1.5 × 4.0 mm) were placed along the buccal cortex (Fig. 2e). A #12 scalpel blade was used to incise the periosteum along the base of the flap to obtain flap release. Placing a gloved finger along the mylohyoid ridge and stretching the thin periosteum and soft tissue was performed to achieve lingual flap release. The flap margins were then advanced over the mesh and closed primarily with 4-0 polyglactin[§§] interrupted and horizontal mattress sutures (Fig. 2f). The patient continued 1 week of antibiotic therapy, a twice daily 0.12% chlorhexidine rinse, and was prescribed a narcotic analgesic. A tapering dose of dexamethasone (4 to 1.5 mg) was prescribed for 2 days.

The patient experienced moderate swelling of the lower face but otherwise healed uneventfully. The grafted site was allowed to heal for 6 months. A CBCT scan was obtained before implant surgery to evaluate the graft healing and select appropriately sized implants (Fig. 2g). The computed tomography (CT) scans revealed favorable bone fill under the mesh, but the density appeared less than the native mandible. Under local anesthesia, an incision was made along the ridge crest. A mucoperiosteal flap was elevated to expose the mesh and fixations screws. The screws were removed, and the edge of the mesh was freed and held with a hemostat to facilitate the dissection from the soft tissue. The fibrous tissue that typically encapsulated the mesh was reflected from the bone. The implant osteotomies were prepared according to the drilling sequence of the manufacturer. The bone density was type 3.[16] Two 4.0 × 8.0 mm dental implants[‖‖] were inserted for submerged healing (Fig. 2h). After a 2-month healing period, the submerged implants were uncovered for prosthetic restoration (Fig. 2i). Periapical radiographs were taken to evaluate the implant healing. The implants were restored with independent cement retained crowns.

Discussion

Although BMPs are involved in bone development, they are pleiotropic growth factors that play a role in the growth and differentiation of various organs. BMPs have been found to be chemotactic for endothelial cells and can also stimulate angiogenesis through the production of vascular endothelial growth factor A by osteoblasts.[17,18]

Previous reports on the use of rhBMP-2 for alveolar bone repair primarily focused on product safety and technical feasibility. Howell et al.[19] evaluated rhBMP-2/ACS for local ridge preservation and augmentation. Clinical results with 0.43 mg/mL rhBMP-2/ACS showed bone fill in the treated extraction sites. Cochran et al.[20] studied the use of 0.43 mg/mL rhBMP-2/ACS in extraction sockets and sites requiring ridge augmentation for future dental implant placement. Implants were successfully placed and restored in 10 patients and were followed for 3 years. No

§§ VICRYL, Ethicon, Johnson & Johnson, Somerville, NJ.
‖‖ Osseospeed TX, Astra Tech.

adverse events were reported, and the implants had stable marginal bone levels and healthy peri-implant tissues.

Fiorellini et al.[15] performed a randomized multicenter study evaluating two concentrations of rhBMP-2 (0.75 and 1.5 mg/mL) in the repair of extraction socket buccal wall defects for dental implant placement. The sockets were filled with rhBMP-2/ACS, and primary closure over the grafted sites was obtained. At 4 months, patients treated with the higher concentration of rhBMP-2 had significantly greater bone augmentation and adequate bone volume for implant placement.

In a recent case series, the use of rhBMP-2/ACS was evaluated for the repair of significant bone defects after removal of maxillary central incisors.[21] The extraction sockets all had >50% buccal bone loss. The sockets were grafted with rhBMP-2/ACS and a small amount of bone substitute. The surgical technique was modified, because primary closure was not obtained over the grafted sockets. Dental implants were inserted after 4 to 6 months of healing, and CBCT scans were used to evaluate the alveolar repair. Dental implants were placed in all grafted sites without the need for additional bone augmentation. A comparison of preoperative and postgraft CBCT scans found a slight loss in alveolar width at the crest of 1.07 mm (range, +0.63 to –2.18 mm). Although primary closure was not achieved over the graft, the healing or induction of bone growth was not compromised. The bone quality of the regenerated tissue was primarily type 3,[16] with all 10 implants well osseointegrated and restored with single crowns.

In this case series,[21] no flap was elevated and no attempt was made to close the soft tissue over the grafted socket. The ACS used as a carrier for the rhBMP-2 allowed connective tissue in-growth and epithelialization over the grafted site. The healing of soft tissue over rhBMP-2-grafted sites appeared to be accelerated as shown in the repair of open tibial fractures with rhBMP-2.[22] This might be attributable to an increase in vascular supply because BMPs can stimulate angiogenesis through the production of vascular endothelial growth factor A by osteoblasts.[17,18]

In a study by Fiorellini et al.,[15] radiographic measurements were taken of cross-sectional CT scan images after extraction and socket grafting. These measurements were repeated 4 months after the socket grafts had healed. An average bone width gain of 3.53 mm at the crest was found in the patients treated with 1.5 mg/mL rhBMP-2. Misch[21] found a slight loss in overall alveolar crestal bone width in 9 of 10 cases with an average loss of 1.07 mm. The disparity in treatment outcomes could be attributed to differences in measurement site selection because Misch took the preoperative width measurements from the palatal bone at the ridge crest to the facial aspect of the root because the facial cortex was absent in most cases.

In the study by Fiorellini et al.,[15] three of 18 (14%) of the 1.5 mg/mL rhBMP-2/ACS grafted sockets required a secondary bone augmentation at implant placement. Comparatively, in the case series presented by Misch in 2010,[21] a small amount of mineralized bone allograft (20%) was mixed with the rhBMP-2/ACS and no additional bone repair was needed at implant placement, thus suggesting that ACS used as a carrier for the BMP molecule has rather poor scaffolding qualities to resist flap compression under pressure and the inclusion of a bulking agent or matrix would provide additional three-dimensional support to the graft.[23]

The traditional methods to repair large extraction socket defects include bone substitutes with barrier membranes or block bone grafting. The use of a barrier membrane often necessitates flap elevation and advancement to obtain primary closure. Exposure of expanded polytetrafluoroethylene membranes can result in infection and a reduction in bone regeneration.[24] Exposed collagen membranes, conversely, lose their structural integrity and resorb rapidly.[25] Block grafting is usually performed as a delayed procedure after soft-tissue healing over the socket to prevent graft exposure and also to minimize the alteration of the gingival anatomy. Performing an immediate bone repair and not having to obtain primary soft-tissue closure over the rhBMP-2/ACS grafted socket offers significant benefits. There is a reduction in the amount of soft-tissue manipulation because no flap is elevated or advanced. This shortens the surgical time and can reduce postoperative pain. It also maintains the normal gingival architecture and facial position of the keratinized tissue.

Fiorellini et al.[15] measured the bone density of healed sockets using CT scans, and a comparison of the new bone formed at 4 months revealed no significant difference in density among the groups (no treatment, ACS alone, and rhBMP-2/ACS). Histologic samples showed remodeling of immature woven bone into lamellar bone. No comments were made regarding the bone quality noted during implant site preparation and placement. In a sinus bone graft study by Boyne et al.,[26] the rhBMP-2-grafted sites had significantly less radiographic bone density than autograft filled sites at 4 months after surgery. This difference was likely attributable to variation in the mechanism of bone formation because the *de novo* bone induction by rhBMP-2 required more time for mineralization. Implants were subsequently inserted after a mean healing period of 6.9 ± 1 months, and the investigators rated the clinical bone quality similar between the autograft and 1.5 mg/mL rhBMP-2 group. This finding was consistent with the bone quality noted in the cases treated. At 4 months of healing, the presence of woven bone provided minimal resistance to drilling. The use of osteotomes and undersizing of the osteotomy could help attain implant stability in softer bone sites. Allowing the rhBMP-2-grafted sockets to heal an additional 1 or 2 months appeared to result in an improvement in bone quality. A longer healing period of ≥6 months appeared to be beneficial when using rhBMP-2 for onlay augmentation. It was unclear whether the addition of a mineralized bone substitute would influence the quality of regenerated bone. It appeared that the resorption of bone substitutes was accelerated by the cellular cascade induced by rhBMP-2.[27]

Although the ACS has been found to be an optimal carrier for the rhBMP-2 molecule, it has poor scaffolding properties to resist flap compression when used for onlay ridge augmentation. Titanium mesh has been proposed as a method to provide support and protection of the rhBMP-2/ACS during healing. Titanium mesh can be used with onlay bone augmentation to protect the collagen carrier and maintain the space for bone in-growth. Herford and Boyne[28] successfully used titanium mesh to maintain the periosteal envelope around large mandibular continuity defects treated with rhBMP-2/ACS. The mesh thickness of 0.2 mm would adequately resist flexing and micromovement during healing and yet be thin enough to mold. The use of titanium mesh for bone augmentation should not be confused with GBR techniques. GBR uses a cellular occlusive barrier membrane to impede soft-tissue penetration and allow the slower growing bone cells to repopulate the osseous defect.[29] Titanium mesh acts as a protective matrix to maintain space and facilitate bone in-growth but is not cell occlusive. Combining rhBMP-2/ACS with a barrier membrane does not seem to provide any additional value and may actually be biologically counterproductive because it occludes cells that may contribute to the bone-forming process and impedes vascularity from the soft-tissue flap.[30-32]

The existing human trials on rhBMP-2/ACS for bone augmentation have not relied on GBR for bone formation.[15,26] The inclusion of a bulking agent or matrix has also been suggested to provide additional three-dimensional support for the collagen sponge.[33] However, the addition of a bone substitute must be weighed against the reduction of the amount of BMP that will be present in the grafted site. A small amount of particulate bone substitute (20%) may provide additional scaffold without significantly diluting the effects of rhBMP-2.[27]

Being a locally acting growth factor, rhBMP-2 induces bone formation at the site of application. It is chemotactic for mesenchymal stem cells, osteoprogenitor cells, and osteoblasts. Preparation of the osseous recipient site is therefore important, because these cells are found in bone marrow and to a lesser degree in soft tissue. The cortex of the recipient site should be generously perforated in multiple sites with a bur to allow access to the marrow. Primary tension-free closure of the soft tissue flaps over the grafted site is necessary to prevent wound dehiscence and early exposure of the mesh. Generally, a "PASS" (for primary wound closure, angiogenesis, space creation, and maintenance and wound stability) principle should be followed.[34] Table 3 is a summary of research on the use of rhBMP-2 for vertical bone augmentation.

Ridge augmentation using rhBMP-2/ACS with titanium mesh offers another approach in the management of the atrophic residual ridge. From a patient's perspective, there are significant benefits because no autogenous bone graft is harvested and thus there is no morbidity associated. The technical procedure is relatively straightforward and as such requires minimal surgical time. However, the ability to manage the surgical flaps to attain tension-free primary closure is still essential. The disadvantages of this technique compared to the use of an autograft include longer graft healing times, softer bone quality, and higher material costs. Although preliminary results appear promising, there are questions regarding the long-term stability of the onlay grafted bone under loading. Additional studies will be helpful in determining specific indications and limitations of this technique.

Conclusions

The use of growth factors offers a new approach to the repair of alveolar defects in preparation for implant placement. The case reports in this article demonstrate the use of rhBMP-2 in the repair of large extraction socket defects and localized ridge augmentation. The collagen sponge carrier appears to have space making limitations that may require addition of a matrix, such as a bone substitute, or use of a scaffold, such as titanium mesh, for graft protection in these applications. The repair of a large alveolar defect associated with a failed tooth may be performed at the time of extraction using rhBMP-2/ACS. This approach does not require the use of a barrier membrane and/or flap manipulation and advancement. Ridge augmentation using rhBMP-2/ACS with titanium mesh offers an alternative method to reconstruct the atrophic residual ridge. The benefits of this technique include relative technical ease and the elimination of autogenous bone harvest with associated morbidity. The disadvantages include long graft healing times, softer bone quality, and higher material costs. ■

Summary

Why is this case new information?	■ This case uses rhBMP/ACS mixed with human allograft for socket repair ■ This case uses rhBMP/ACS mixed with human allograft and supported with titanium mesh for horizontal and vertical bone augmentation
What are the keys to successful management of this case?	■ rhBMP-2 was used to accelerate soft tissue healing, minimize healing time and potential postsurgical infection, and promote cell migration and early bone formation ■ Human allograft and titanium mesh were used to create and maintain the space that is needed for bone to grow ■ The ``PASS'' (primary wound coverage, angiogensis, space, and stability) principle was followed
What are the primary limitations to success in this case?	■ Lack of primary wound closure attributable to flap tension ■ Lack of angiogenesis ■ Lack of space creation and maintenance ■ Lack of wound and implant stability

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