SELECTED READINGS

IN

ORAL AND

MAXILLOFACIAL SURGERY

BMP IN RIDGE
RECONSTRUCTION
FOR DENTAL IMPLANTS

David Hoffman, DDS and
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BMP IN RIDGE RECONSTRUCTION FOR DENTAL IMPLANTS

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INTRODUCTION

Bone grafting in maxillofacial surgery is a method of creating or transferring bone to the craniofacial skeleton. The indications for bone grafting to these structures for construction or reconstruction are listed in Table 1. Surgeons have a dizzying array of options when it comes to treatment planning defects of the craniofacial skeleton. For instance, in a horizontally-deficient anterior maxillary alveolar defect one could use 1) an autogenous block graft from the chin, ilium, or ramus, 2) an allogeneic block graft, an allogeneic particulate graft placed under a resorbable collagen membrane or under titanium mesh, 3) an autogenous cancellous graft utilizing either a resorbable membrane or mesh, or 4) recombinant human bone morphogenetic protein -2 (rh-BMP-2) used off-label. Similarly, there are a wide variety of reconstructive options for continuity defects of the mandible, including 1) autogenous corticocancellous block grafts, 2) particulate cancellous bone grafts (placed in either an allogeneic bone crib or an alloplastic mesh crib), 3) microvascular fibula free flap, or 4) off-label rhBMP-2. A summary of these grafting materials is in Table 2. As we look to the future, engineering constructs from stem cells will provide even more options.1

The purpose of this article is to review the biology of recombinant human bone morphogenetic protein-2 (rhBMP-2) and examine its use in the context of normal bone development and healing. We will also discuss the on- and off-label uses of rhBMP-2 in oral and maxillofacial surgery and present some illustrative cases.

TABLE 1: INDICATIONS FOR BONE GRAFTING

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<tr>
<td>1.</td>
<td>Provide sufficient bone for the placement of dental implants.</td>
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<td>2.</td>
<td>Reconstruction of bone defects secondary to trauma, infection or ablative surgery</td>
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<td>3.</td>
<td>Reconstruction of congenital facial deformities</td>
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<td>4.</td>
<td>Reconstruction of bone defects created during orthognathic surgery</td>
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<td>5.</td>
<td>Preservation of tooth extraction sockets</td>
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TABLE 2: SUMMARY OF GRAFTING MATERIALS

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<td><strong>AUTOGENOUS</strong></td>
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<td>Free bone grafts</td>
<td>Microvascular free flaps (free bone flap + muscle/skin)</td>
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<tr>
<td><strong>ALLOGENIC</strong></td>
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<td>Freeze dried bone</td>
<td>Demineralized freeze dried bone</td>
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<td><strong>XENOGRAFT</strong></td>
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<td>Bovine</td>
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as a template that is resorbed as bone is mineralized by osteoblasts. This process forms most of the bones of the skeleton. Intrapemembranous bone formation, seen primarily in the craniofacial skeleton, results from cells in condensed mesenchyme differentiating into osteoblasts that then produce the mineralized matrix. Both processes of bone development involve multiple cell types and signaling molecules that either up-regulate or down-regulate such processes as cell proliferation, differentiation, mineralization, and apoptosis.

During bone healing, a similar set of cells and signals are required. Primary bone healing occurs when the two bone edges of a fracture are tightly aligned and made completely stable (as in rigid fixation). Healing occurs through the action of osteoclasts forming a “cutting cone” and the subsequent recruitment of osteoblasts to form new Haversian systems.

Secondary bone healing occurs with sequential formation of a cartilaginous callus, osteoid, and finally, bone mineralization by osteoblasts and remodeling. This sequence typically occurs when rigid fixation is not employed. At the site of bone injury a blood clot forms followed by inflammation, then angiogenesis begins, and cartilage is first produced and then removed as bone is formed. The callus functions to stabilize the injury so that ossification can proceed. Finally the bone is remodeled. Multiple growth and differentiation factors and inhibitors are required for this elaborate, yet well-controlled process.

Autogenous or allogeneic cortical block grafts heal primarily through creeping substitution. As vascularization of the block occurs, osteoclasts resorb portions of the graft and new bone is produced. Minute amounts of BMP-2 are released from the cortical bone, but not enough to cause robust osteoinduction.

Autogenous particulate cancellous grafts transfer mesenchymal stem cells (MSC), osteoblasts, and hematopoietic cells such as platelets. Many of these cells survive and the platelets undergo release of multiple growth factors that initiate chemotaxis of inflammatory cells, are mitogenic, and are angiogenic. However, these factors are not osteoinductive by themselves. Platelet rich plasma has been introduced into clinical care but there remains conflicting evidence as to its efficacy.

BONE MORPHOGENETIC PROTEINS

In a landmark article, Urist demonstrated that decalcified bone matrix implanted into muscle pouches in rabbits and rats and in skeletal defects in humans results in bone formation at the site of implantation. He hypothesized that a substance, which he named bone morphogenetic protein, was osteoinductive, i.e., cells capable of differentiating into bone were attracted to the site of implantation and were induced to form new bone. Today we know these cells to be mesenchymal stem cells.

Reddi and Huggins, in 1972, demonstrated that this induced bone formation goes through the same stages of endochondral bone formation that are observed during normal bone development and healing. BMP-2 can also initiate direct or intramembranous bone formation.
BMPs are critical signaling factors responsible for the body plan, limb patterning and controlling craniofacial skeleton development, the last being controlled by the activity of BMPs on cranial neural crest cells. Additionally, Korchnylnskyi and coworkers, using micro-array analysis, demonstrated that over 100 genes are either up-regulated or down-regulated by BMP binding during osteoblast differentiation.

BMPs are members of the TGF-beta family that bind to specific cell-membrane receptors that activate the intracellular SMAD signaling pathway. The SMADs are specific intracellular proteins that either up-regulate or down-regulate specific genes. Control mechanisms are in place to down-regulate BMP activity. For example, Noggin, a BMP antagonist, regulates cranial suture fusion.

BMP-2 attracts mesenchymal stem cells and promotes their proliferation and differentiation into osteoblasts. BMPs also attract monocytes that then release cytokines and growth factors that, in turn, induce angiogenesis and additional proliferation of mesenchymal stem cells.

The amino acid sequences of a highly purified extract from bovine bone was used to manufacture a complementary DNA clone by Wozney, et al. These authors further demonstrated that these BMP clones (corresponding to BMP1, BMP2a and BMP3) were osteoinductive and induced cartilage and bone formation. Today there are over twenty BMP clones that are members of the transforming growth factor Beta family and only a few, notably BMPs 2 -7 and 9, induce bone formation. BMPs 2, 6 and 9 induce the differentiation of mesenchymal stem cells while the other BMPs are involved in the conversion of preosteoblasts into osteoblasts, suggesting that BMPs 2, 6, and 9 would be more effective clinically. Recombinant human BMP 2 and BMP 7 are manufactured using plasmid technology and are commercially available.

Because recombinant human bone morphogenetic protein -2 (rhBMP-2) is cleared from the circulation in minutes, it must be applied locally. The amount of osteoinduction observed is concentration-dependent at the site where bone is required. The dose of rhBMP-2 in humans is 1.50 mg/ml of sterile water. Because rhBMP-2 is a protein that requires reconstitution prior to use with sterile water, a carrier material must be used. The protein must bind to the carrier and ideally have the appropriate release kinetics to attract MSCs (mesenchymal stem cells) to the site and then promote their proliferation and differentiation.

The carrier should be porous to promote in-growth but then resorb as bone is deposited. Numerous carriers have been studied and currently rhBMP-2 is carried by a bovine absorbable collagen sponge (ACS). The bovine ACS has been in use for over 25 years and has an excellent safety record. rhBMP-7 is carried by particulate bone-derived collagen matrix. The dosage of rhBMP-7 that is recommended for long bone fracture healing is 3.5 mg reconstituted in 1 g of type-1 bovine collagen. It should be noted that rhBMP-7 is not approved for maxillofacial use.

Platelet derived growth factors such as PDGF and TGF-beta are growth factors that
cause cells to divide. BMPs are differentiation factors that cause MSCs to differentiate into osteoblasts. There is no evidence that combining these together will result in a more robust bone reconstruction. In fact there is evidence to the contrary; these different types of factors may antagonize each other.19,20

APPROVED INDICATIONS

Recombinant human bone morphogenetic protein-2 (rhBMP-2) is currently approved by the Food and Drug Administration for sinus lifts to facilitate implant placement and extraction socket augmentation. In a Phase I clinical trial, Boyne, et al. demonstrated that 0.43 mg/ml rhBMP-2 placed on an absorbable collagen sponge induced new bone formation in all 11 patients enrolled.21 However, the amount of bone was inadequate in 3 patients, suggesting that a higher dose was needed.

In a Phase II randomized clinical trial 0.75mg/ml and 1.5mg/ml of rhBMP-2 were compared to an autogenous bone graft to determine safety and efficacy.22 A total of 48 patients were enrolled in this study; 18 patients received 0.75mg/ml, 17 patients received 1.5mg/ml and 13 patients received a bone graft. The bone graft group was divided into autograft alone and autograft plus allograft. All three groups had similar amounts of bone formation, and patients who received 1.5mg/ml of rhBMP-2 had more rapid induction of bone formation. The adverse event data collected on during this clinical trial demonstrated safety of rhBMP-2 at both dosages.

The Phase III sinus-lift clinical trials randomized 78 patients to the bone graft group and 82 patients to the 1.5mg/ml rhBMP-2/ACS group. Both groups had similar amounts of additional bone height. However the bone was denser in the rhBMP-2/ACS group. Again, the adverse event data demonstrated safety in the rhBMP-2 group but donor site morbidity in a significant number of patients receiving an autograft.23

A clinical trial was also performed evaluating extraction socket augmentation in patients with buccal wall defects.24 Patients were randomized to one of four groups: 1) 0.75mg/ml of rhBMP-2/ACS, 2) 1.5mg/ml rhBMP-2/ACS, 3) ACS alone, or 4) no treatment. The 1.5mg/ml rhBMP-2 delivered on an ACS was most efficacious and allowed implant restoration.

In an earlier study that evaluated safety, Cochran, et al. followed 12 patients who received 0.43mg/ml for extraction socket grafting or local ridge orientation for three years.25 No adverse events were reported in the 12 patients enrolled in the study. Ten patients were functionally restored with implants.

Recombinant human bone morphogenetic protein 2 is also FDA approved for spinal fusion at one level between L2 and S1 in skeletally mature individuals and for treatment of acute open tibial shaft fractures in conjunction with intramedullary nailing.

OFF-LABEL USES OF RHBMP-2/ACS

In oral and maxillofacial surgery there have been numerous case reports and case se-
ries of off-label uses in both skeletally mature and immature patients. Continuity and segmental defects of the mandible, horizontal and vertical deficiency of the maxilla and mandible, and alveolar cleft repair in children are the more common off-label uses. However, there have been no controlled, randomized, prospective studies comparing the efficacy of rhBMP-2/ACS to either autogenous bone or allogeneic bone for these uses. No clinical trials have been performed in the pediatric population. It should be noted that rhBMP-2 is contraindicated in pregnancy or women who expect to become pregnant within one year of use, and in reconstruction of malignant lesions.26

**Mandibular Defects**

Continuity defects of the mandible were successfully reconstructed in non-human primates with rhBMP-2 by Boyne in 1996.27 In 2008, Herford and Boyne, in a retrospective case series, reported successful bone regeneration of critical size continuity defects of the mandible in 14 patients when using rhBMP-2 alone. They believed that maintenance of a periosteal envelope is critical for the successful use of rhBMP-2 in these patients.28 This series of patients was selected from a larger group who received rhBMP-2.

In a more recent paper, Herford combined rhBMP-2 with demineralized bone (DMB) to successfully reconstruct mandibular defects. He believed the addition of DMB prevented compression of the collagen sponge carrier and allowed for faster bone formation and consolidation.26 Furthermore, Herford used a thin plate or titanium mesh at the superior border of the reconstruction to maintain the height and shape of the alveolus.

However, Carter, et al. reported no bone formation in two of four patients with continuity defects treated with rhBMP-2.29 Kraut, more recently, also demonstrated no bone formation in three patients who received rhBMP-2 for large continuity defects of the mandible. All three patients subsequently had successful autogenous bone grafts to reconstruct their defects.30

In 2011, Herford, et al. reviewed the literature on the use of rh-BMP in mandibular reconstruction.31(See also Selected Readings in Oral and Maxillofacial Surgery, Vol. 16, #6) A total of 37 patients were treated with rhBMP (one patient received human BMP and ten patients received BMP-7) with a success rate of 86.5%. Herford and his co-authors concluded that because of the failure rate and the small number of clinical studies, autogenous bone grafts might still be preferable to growth factors. He further stated that the use of rhBMP-2 is a promising technique for mandibular reconstruction.

Herford also opined, in a clinical controversies article, for the use of BMP due to the absence of donor site morbidity, reduced operating time, and reduced hospital length of stay.31 Bell and Gregoire, in the opposing opinion, argued for vascularized grafts, in conjunction with malignant and radiated patients or defects greater than 6 cm and as part of a primary reconstruction.32 To date the question of BMP verses an autogenous iliac hip graft remains unsettled, but its use in non-malignant and infection-free cases seems very promising.
Case 1: Mandibular Defect

A 58 year-old male with a keratocystic odontogenic tumor of the mandible underwent a segmental resection extending from the right first molar to the left canine. (Fig.1) After excision of the lesion the inferior border of the mandible was intact. A bone plate was used to prevent a fracture and soft tissue coverage was obtained.

Staged reconstruction consisted of a combination of rhBMP-2/ACS and DMB and the use of an absorbable bone mesh (KLS). Immediate postoperative imaging confirmed a gain of 10 mm of vertical height. No post-op denture was used. After 3 months the absorbable plate lost its strength and the new bone partially resorbed.

The graft was repeated with rhBMP-2/ACS contained within titanium mesh that was secured with screw fixation. Six months later the titanium mesh was removed and 6 implants placed. Four months later the implants were uncovered and successfully restored; they have been in function for over 4 years.

This case illustrates the need for structural support to maintain the height of the desired reconstruction.

Atrophic Mandible

Recombinant human BMP-2/ACS can be used in reconstructing the atrophic mandible and maxilla. The technique is similar to that described separately by Buser and von Arx, however instead of using autogenous or allogeneic bone under the mesh, rhBMP-2/ACS is used. Because of the compressibility of the absorbable collagen sponge carrier, titanium mesh, allogeneic bone, autogenous cancellous bone harvested form the ilium through a small incision or trocar, and tenting screws can be used to maintain the three-dimensional reconstruction in size and shape. Stereolithographic models derived from CT scans assist in planning the reconstruction and in adapting the titanium mesh.

Figure 1. Case 1. A. Patient with a mandibular OKC that requires ablation. B. Treated with BMP, demineralized freeze-dried bone (DFDB), and titanium mesh. C. Final restorations in place.
Case 2: Atrophic Mandible

A 50-year-old female presented with failing implants and severe mandibular atrophy. The initial treatment was removal of the failing implants, debridement of the granulomatous tissue, and allogeneic bone grafting covered by a resorbable membrane to allow the ridge and soft tissue to heal and mature. Several months were allowed for the gingiva to heal and be suitable for definitive surgery. Using a crestal incision, a mucoperiosteal flap was elevated and undermined visualizing the nerve, and allowing a tension free closure.

Several pieces of titanium mesh were adapted so that the lateral pieces could be placed with a combination of rhBMP-2/ACS and DMB. Tenting screws were placed in a vertical direction. Two screws for each sheet of titanium were used placed from the lateral aspect.

Using multiple sections of mesh allows the surgeon to place more graft under the mesh after it is secured. This cannot be done if one single contoured mesh is used. One of the advantages of the tenting screws is that they will make sure there is sufficient vertical height achieved with the grafting procedure. The lingual mucosa must be elevated to ensure that the titanium mesh covers the lingual border of the mandible. It is in this area that the mucosa is thin and placement of a resorbable membrane just on the lingual aspect may prevent dehiscence. The use of a resorbable membrane to cover the entire mesh is not warranted because it has the potential to prevent the attraction and migration of MSCs.

Figure 2. Case 2. A. Patient with failing implants and secondary mandibular atrophy. The implants were removed, and the soft tissue was allowed to heal. B. the BMP and mesh used to reconstruct the mandible. C. the implants in place awaiting prosthetic restorations.
After 6 months a crestal incision was used to expose and remove the mesh and place six implants. Four months later the implants were uncovered and restored with a fixed prosthesis.

Denture use is limited during the first six weeks after the debridement and the reconstruction. A tension-free closure is critical and trauma to the area must be minimized. Mesh exposure is treated with local wound care and the mucosa is allowed to granulate in under the exposed mesh. There will frequently be sufficient bone for implants.

Bone formation will not be apparent on radiographs until the fifth or sixth month. To date very little has been published on the technique. Because of potential swelling around the airway, care must be taken when using rhBMP-s/ACS in the posterior mandible and in bilateral cases. There have been no reports of airway embarrassment after mandibular or maxillary reconstruction. The reason for the increased swelling with rhBMP-2 is unclear, however it is postulated that there is a cytokine release causing the inflammation. The use of peri-operative steroids may help in limiting this response, but in most cases it is a transient event seen in the first week that quickly subsides.

**Posterior Mandible**

Situations arise when only the posterior mandible is missing teeth and is atrophic. The most common problems are either insufficient bone height above the mandibular nerve or a thin, knife-edge ridge. For minor defects allogeneic or autogenous block grafts with or without a resorbable membrane or a tunnel technique with allogeneic particulate bone are predictable. Autogenous bone can result in donor site morbidity and increased length of surgery. Vertical augmentation can be challenging with these techniques. Vertical alveolar distraction has also been described but also requires a minimum amount of bone to distract, and has other complications including fracture, vector control issues, and possible nerve injury.

rhBMP-2 for posterior mandibular ridge reconstruction can also be used. The following cases describe the basic principles of rhBMP-2 grafting. It is off-label use and has the distinct advantages of no donor site and possible utilization in severely atrophic situations.

**Case 3: Posterior Mandible**

A 25-year old-female had a posterior mandibular defect following the resection of a myxoma. After the tumor was resected, the soft tissue was allowed to heal. The resultant deficient posterior mandibular ridge was reconstructed with rhBMP-2, allogeneic bone and titanium mesh. The graft was allowed to mature and develop bone with the prescribed 6-month waiting period. The mesh was then removed and implants were placed.

Although this case healed uneventfully, thin lingual mucosa can result in dehiscence of the lingual portion of the mesh. To prevent that scenario one can substitute the titanium mesh with 0.4 mm polyethylene sheeting and reinforcement of the lingual mucosa with a double layer of resorbable membrane. Tenting screws are also an option. The mesh or sheeting is first customized for the appropri-
Figure 3. Case 3. A. A medical model of a patient with a myxoma, and B. then reconstructed with a BMP and mesh graft. C. The cone-beam CT scan shows bone formation at 6 months, and D. implants placed into the new bone formation leaving the mesh in place.
ate shape, and then filled with grafting material. Screws are placed on the lateral aspect. More grafting material is then inserted once the mesh or sheeting is stable. A vestibular incision (with care taken to protect the mental nerve) can be utilized instead of a crestal incision. This moves the incision line away from the top of the mesh.

Maxillary Reconstruction

The maxilla’s unique anatomy makes finding adequate alveolar bone for implant placement difficult. Tooth loss in the anterior maxilla results in resorption of the alveolus in a superior and posterior direction. There is frequently insufficient height and width to support dental implants. The posterior region can have similar problems but generally can be solved with a sinus lift. More complex problems arise with defects that have no underlying bone, as in the case of tumor resection, traumatic injuries, alveolar clefts, infection, and oral-antral or oral-nasal communications.

Case 4  Anterior Maxilla Reconstruction

A 55-year-old female was referred for dental implants to the left maxilla replacing five teeth. Clinical exam and a cone-beam CT scan revealed a knife-edge ridge that could not support dental implants. Treatment options included an onlay graft from intraoral sites, a ridge-splitting osteotomy with an interpositional graft, or rhBMP-2 ridge reconstruction.

Surgical treatment utilized a crestal incision, and elevation and releasing of the mucoperiostial flap to allow for a tension free closure. The mesh was in two sheets and contoured to provide ample width. The grafted material consisted of rhBMP-2/ ACS and Grafton (Medtronic, Inc., Minneapolis, MN). The mesh was stabilized with two screws per
sheet and a tension free closure was obtained. After 6 months the mesh was removed and three implants were placed. Four months later the implants were restored. A 4-year follow-up showed stable results.

Case 5  Maxillary Defect and Oral Nasal Communication

A 64 year-old male presented with the following problems in the maxilla: failing anterior dental implants, knife-edge ridge, and two oral-nasal communications.

Treatment consisted of removing the failing implants, debridement, and reconstruction with rhBMP-2/ACS, and titanium mesh. Six months later four implants were placed at the time of mesh removal. Four months following placement the implants were uncovered and restored. Four years later the implants have remained integrated and the prosthesis is functioning.

Case 6 : Maxillary Reconstruction

This patient underwent a similar maxillary reconstruction as the preceding patient. Despite a tension free closure, the titanium mesh became exposed but was not infected. New bone covered with soft tissue formed under the exposed mesh. At six months the mesh was removed and implants were successfully placed. The tissue and bone formed under the mesh, and implants could be placed and restored. Von Arx also reported dehiscence when using mesh with autogenous bone.35

Alveolar Cleft Defects

The use of rhBMP-2 for alveolar cleft grafting is one of the few off-label uses that has been described in the literature. In this clinical setting rhBMP-2/ACS is frequently used in conjunction with allogeneic bone.
Boyne, in 1998, created bilateral palatal clefts in non-human primates and three months later implanted either autogenous bone or 0.43mg/ml rhBMP-2 in an absorbable collagen sponge. He reported successful bone healing in both groups concluding that rhBMP-2 may replace autogenous bone grafting in the cleft population.\textsuperscript{36} Recent reports have demonstrated the efficacy of rhBMP-2 for the treatment of alveolar clefts in children.\textsuperscript{37-45} However, there are no prospective, randomized clinical trials comparing rhBMP-2/ACS to autogenous bone for alveolar cleft reconstruction.

In a retrospective chart review, Francis et al. compared 36 patients who received rhBMP-2/ACS with demineralized bone matrix putty to 19 patients who underwent conventional iliac bone grafting of their alveolar clefts.\textsuperscript{45} Ten of the 36 patients had previously failed an iliac bone graft. The mean follow-up was 21 months. The Bergland and Chelsea scales were used to grade the amount of bone formation seen on radiographs.\textsuperscript{46,47} The rhBMP-2 patients had a 97.2% success rate compared to an 84.2% success rate in the autogenous bone graft patients. The autogenous bone graft group also had a greater incidence of infection at the recipient site that was statistically significant. Despite the cost of rhBMP-2/ACS, the authors also concluded that its use was cost effective.

Currently the only carrier approved for rhBMP-2 is a bovine absorbable sponge. Recently Neovius et al. reported on a small prospective clinical trial using rhBMP-2 carried by a hyaluronan-based hydrogel.\textsuperscript{48} Their initial two patients after receiving 50ug of rhBMP-2/ml of hydrogel did not form bone; the concentration was increased to 250ug/ml of carrier. Severe gingival swelling was seen in this group and the study was stopped. Bone formation was 59% and 33%. Interestingly the CT results at six months were similar to patients receiving autologous bone (29%, 48%, and 69%). Unfortunately the sample sizes were small. Critical review of the “successful” six month CT scans presented demonstrates dubious success at best.

We presented our combined experience at the AAOMS meeting 2012 based on 20 cleft patients, 15 unilateral and 5 bilateral. Sliding mucogingival flaps were used for closure, along with repair of the nasal floor. All cases showed good bone formation on CT or plain radiographs, with up to 4 years of follow-up. The use of rhBMP-2 in a growing child remains controversial, however the latest orthopedic literature does not contraindicate its use.

Case 7: Alveolar Cleft Defects

A 7-year-old female with a left unilateral cleft lip with an unrepaired alveolar cleft was referred for treatment. The surgical tech-
SAFETY AND COMPLICATIONS

The clearance of rhBMP-2 into the circulation when released by the sponge is seven minutes. In addition approximately 5% of patients developed antibodies to the rhBMP-2. There have been no reported osteosarcomas in patients who received rhBMP-2/ACS. In an in-vitro and in-vivo study using nude mice and human oral squamous cell carcinoma cells cultured with human mesenchymal stem cells, there was no evidence that rhBMP-2 increased proliferation of a squamous cell carcinoma line or caused increased angiogenesis. However, in studies involving a lung cancer cell line, increased growth and angiogenesis after addition of bone morphogenetic protein-2 was demonstrated. It should be stressed that all of these studies involved in vitro cancer cell lines.

Ectopic bone formation has been observed in a rat femur model. This has not been reported in maxillofacial use in humans or in pediatric cases.

Woo, a medical officer with the Food and Drug Administration, reported that 83 adverse events were recorded by the FDA’s Manufacturer and User Facility Device Experience (MAUDE) in 2012. Fifty-five of the 83 reports were for off-label uses such as alveolar cleft repair and mandibular reconstruction. Of the 83 reports, there were 28 reports of local edema and pain, 14 surgical site infections, and 15 graft failures. Of the graft failures, 12 were in the off-label use group and 3 were in the approved group. There were 5 reports of pseudoarthrosis in the off-label group and none in the approved group.
Figure 8. Data from a poster presented at AAOMS meeting 2010. The data illustrates the amount of bone that was maintained from patients with BMP grafts and titanium mesh described above. Showing a better than 85% increase in width and over 90% increase in height in the bone formed on the alveolar ridge with BMP and mesh.

While these reports are certainly interesting, adverse events are probably under-reported by clinicians and the total number of patients receiving rhBMP-2/ACS for maxillofacial indications is unknown. As of 2013, it has been estimated that over 1.5 million patients worldwide have received rhBMP-2/ACS for orthopedic and maxillofacial indications. (Buxton, A, personal communication) Furthermore, the complication rates at both the donor and the recipient site for autologous bone grafting for similar indications are not reported to MAUDE but have been evaluated in a number of clinical trials.

Carragee, et al. in a review article compared published data from industry sponsored clinical trials to that reported to the FDA and in subsequent published reports in spinal fusion surgeries.53 They concluded that the incidence of adverse events was 10-50 times higher than reported from industry-sponsored studies. It should be noted that these complications include serious cervical edema, osteolysis, retrograde ejaculation from lumbar fusions, infection, and cancer. Increased cancers were seen in the AMPLIFY clinical trial (an increased dose of rhBMP-2 in a different carrier) compared to the control group. However, while more than the control group it did not exceed the expected cancer incidence.54 It should be noted that this article only addressed the use of rhBMP-2 in spinal surgery.

In response to this article the Yale University Open Data Access (YODA) Project was provided full data from Medtronic from all trials of rhBMP-2 for re-analysis.55 This extensive review stated there might be an increased risk of cancer; however the incidence of cancer in both rhBMP-2 and autogenous bone graft groups were low, making conclusions difficult to draw. Additionally, many of the complications described by Carragee, et al. were not from prospective randomized studies and therefore no conclusions can be drawn.53

TECHNICAL PEARLS

The use of rhBMP-2 and ACS for reconstruction of the maxillary and mandibular ridges for dental implants appears to be a biological sound technique. Some technical guidelines that may be of help when using this material are:

- Mesh must be stabilized with screws
- At this time only the absorbable collagen sponge is approved as the carrier for rhBMP-2
• rhBMP-2/ACS can be combined with demineralized bone to increase volume and rigidity

• Tension free closure should be obtained

• Try to avoid loading the reconstruction with a denture for at least six weeks

• Allow six months for bone formation

• Mesh exposure should be treated with local wound care such as oral irrigations

CONCLUSIONS

The FDA has approved rhBMP-2/ACS for sinus augmentation and tooth extraction socket preservation. However, there are many alternative materials that can be used for both these situations and the cost of rhBMP-2/ACS makes it a less attractive option. Other uses of rhBMP-2, such as continuity or segmental defect reconstruction, onlay reconstruction of the alveolus, and alveolar bone grafting are off-label and not approved by the FDA. Therefore, the clinician is obligated to have a thorough discussion with the patient.

There have been no prospective clinical studies comparing rhBMP-2/ACS with either autogenous or allogeneic bone for the off-label indications discussed in this article. Based on case studies and the clinical trials performed for sinus lifts and extraction socket grafting, off-label use of rhBMP-2 appears to be safe in the maxillofacial region. Our collective experience when using rhBMP-2/ACS for maxillary or mandibular reconstruction and alveolar cleft grafting compares favorably with the literature and autogenous bone grafting. However, rhBMP-2/ACS needs structural support because tissue contraction will act as an external force. It is envisioned that additional carriers will become available that will assist in maintaining the desired three dimensional reconstruction. It is also anticipated that multiple growth factors delivered in the correct temporal sequence will also result in a more robust reconstruction.

Dr. David Hoffman is currently the director of Oral & Maxillofacial Surgery at Staten Island University, where he has a hospital-based practice. He is a graduate of the University of Wisconsin, where he received his BS degree, and spent 2 years as a NIH fellow in the medical school. He received his dental degree from NYU College of Dentistry, and completed his oral and maxillofacial training at Parkland Memorial Hospital, Southwest Medical School in Dallas, Texas. He practices a full scope of oral and maxillofacial surgery, and is affiliated with the Kings County OMFS training program. He is also the medical director for Healing The Children, and has been traveling with many medical teams to underdeveloped countries providing mostly cleft surgery for the past thirty years. In addition, he is the director of both the Staten Island Hospital and Maimonides Medical Center cleft lip and palate teams. He lectures on a variety of topics, including dental implants, cleft lip and palate surgery, and TMJ surgery. He also is a sculptor and has taught a class in sculpting the face at the annual AAOMS meetings. He is board certified in OMFS, and holds teaching appointments at several of the New York City training programs.
**Dr. Sidney B. Eisig** is the George Guttman Professor of Craniofacial Surgery and Chair of the Section of Hospital Dentistry at Columbia University College of Dental Medicine and Chief of the Hospital Dental Service at New York - Presbyterian/Columbia University Medical Center. He received his dental degree from New York University and then completed his general dental internship and residency in oral and maxillofacial surgery at Long Island College Hospital in Brooklyn, and The New York Hospital - Cornell Medical Center, respectively. Dr. Eisig then completed an oral and maxillofacial surgery fellowship at Shock Trauma and the University of Maryland Hospital. He has a particular interest in orthognathic, craniofacial and cleft palate surgery, maxillofacial pathology and reconstruction, and pediatric oral and maxillofacial surgery. His current research focuses on the use of stem cell engineering to reconstruct the facial skeleton.

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