Applications of Bone Morphogenetic Protein-2: Alternative Therapies in Craniofacial Reconstruction

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Abstract: Large defects of the craniofacial skeleton can be exceedingly difficult to reconstruct since autologous bone grafts are limited by donor site morbidity and alloplastic implants have low biocompatibility. Bone morphogenetic proteins (BMPs) in craniofacial reconstruction have been used with mixed outcomes and complication concerns; however, results for specific indications have been promising.

In alveolar clefts, cranial vault defects, mandibular defects, and rare Tessier craniofacial clefts, BMP-2 impregnated in collagen matrix was looked at as an alternative therapy for challenging cases. In cases where structural support was required, BMP-2 was used as part of a construct with bio-resorbable plates. Demineralized bone was added in certain cases.

The authors described specific indications, detailed surgical techniques, and a review of the current literature regarding the use of BMP-2 in craniofacial reconstruction. BMP-2 is a viable option for craniofacial reconstruction to decrease donor-site morbidity or when alternatives are contraindicated. It is not recommended for routine use or in the oncologic setting but should currently be reserved as an alternative therapy for complex cases with limited options.

Bone morphogenetic proteins are a promising, emerging option for complex craniofacial reconstruction. Future directions of BMP-2 therapies will become apparent as data from prospective randomized trials emerges.

Key Words: Alveolar reconstruction, BMP, cleft, cranial vault defect, craniofacial, mandibular defect

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When faced with a difficult case or revisionary surgery, it is important to have multiple options for skeletal reconstruction. Bone morphogenetic protein 2 (BMP-2) with inductive bone therapy offers an alternative to traditional osseous reconstruction which uses bone grafts or alloplast.[1–3] However, indications for the use of BMP-2 are evolving and precautions should be taken.[4] This review catalogs current literature and operative indications for the use of BMP-2 therapy and documents techniques for its use.

Critical-sized defects of the craniofacial skeleton are defects that will not heal primarily and can be particularly challenging to reconstruct. These bony defects may be congenital, or due to neoplasms or trauma. Traditionally, reconstruction is performed with autologous bone grafts or alloplastic implants, including custom computer-aided design and computer-aided manufacturing implants. Although autologous bone remains the gold standard, its use has certain limitations, including blood loss, and donor site morbidity.[5,6] In the pediatric population, split-thickness cranial bone grafts are possible but may be technically challenging because of an underdeveloped diploic space.[7–13] Although alloplastic implants obviate the need to harvest autologous tissue, their low biocompatibility can result in various complications including periimplant infection, prolonged wound healing and exposure, and induction of an immune response.[14–17] In addition, non-resorbable alloplastic implants may impede growth and should not be used in the growing craniofacial skeleton.[18] To address some of these shortcomings, bioresorbable plates and screws have increased in popularity,[19] however their lack of biocompatibility, albeit temporary, remains an issue.

In an effort to provide an adjunct for bone healing, the Food and Drug Administration approved the use of BMP in spinal surgery in 2002. Subsequently, BMP has emerged as a promising option for craniofacial reconstruction because of its bone induction qualities.

This overview will focus on the off-label use of BMP-2 in 4 craniofacial operative procedures: alveolar cleft repair (both primary and secondary), cranial vault defect reconstruction, mandibular skeletal defect reconstruction (with supportive crib), and rare Tessier cleft osseous repair. This overview will review the supporting literature, indications, techniques, and cautionary notes for each of these applications of BMP-2, to guide its use in craniofacial reconstruction. All patient photos are used with consent.

BONE MORPHOGENETIC PROTEINS PROPERTIES AND EFFECTS

Bone morphogenetic proteins, namely BMP-2 and BMP-7, are members of the TGF-β gene family that play an important role in stimulating osteoblast activity and promoting bone formation and fracture repair.[20–34] They do so by way of transmembrane serine/threonine kinase receptors and intracellular signaling proteins called Smads.[35,36] Their ultimate downstream effect is to induce differentiation of osteoprogenitor and mesenchymal stem cells into functional osteoblasts.[37] In vivo animal studies have successfully used BMP to improve healing in a variety of bone injury models.[38–41] In humans, BMP has proven efficacious in both orthopedic and oral surgery applications (spinal fusion procedures, repair of complex long bone fractures,[42–44] and in sinus lift surgery in preparation for dental implants).[45,46] Although outcome studies for BMP-2 in craniofacial reconstruction are relatively sparse, early studies have shown positive results.[2,15,47–56]

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Although BMP has shown promising early results, there are known side effects associated with its use. It is currently Food and Drug Administration-approved for use in sinus augmentation, spinal fusion, and tibial shaft fractures. Its early use in spinal fusion procedures was shown to have higher overall complication rates,[57–59] however, none of these studies compared patient demographics of those who received BMP and those who did not. Additionally, there have been reports of significant local tissue swelling associated with BMP requiring removal of the BMP implant.[60,61] There have also been concerns raised about ectopic bone formation, although all reports have been asymptomatic or had no clinical sequela.[62,63] There is now emerging data that many of these side effects are likely dose[64] and delivery system[65,66] dependent, and lower doses may be equally efficacious.[67] Lastly, the potential carcinogenic effects of BMP have been explored, but no definitive link has been established.[68,69]

BONE MORPHOGENETIC PROTEINS DELIVERY SYSTEMS

Delivery systems play an important role in the use and applications of BMP. Their main role is to maintain the growth factors in the required location at the necessary concentration to induce bone formation while minimizing effects on surrounding and distant tissue (i.e., ectopic bone formation). Ideally, carriers should have adequate porosity to enable angiogenesis and infiltration of cells and be biodegradable.[70] Several carriers have been used including biodegradable polymers such as polylactic acid-*p*-dioxanone-polyethylene glycol,[71,72] Poly(lactic-co-glycolic acid) (PLGA).[73,74] A significant disadvantage to the use of synthetic polymers is the risk of an inflammatory response due to products of degradation.[73] This has prompted the use of collagen and other natural polymers as an alternative.

Collagen has emerged as a promising delivery system for BMP. Collagen sponges are versatile and biodegradable. They hold BMP and only release it locally. The concentration of BMP that a sponge carries can also be varied and depends on factors such as sponge mass, soaking time, protein concentration, and so on.[75] Although they have increased in popularity, collagen sponges may be complicated by immunogenic reactions. To minimize these risks, natural origin polymers such as starch-based polymers, alginates, silk, fibrin, hyaluronans, as well as ceramics (hydroxyapatite, calcium phosphates), and micro- and nanoparticles are being explored.[76–78]

CLINICAL PRESENTATIONS

Alveolar Bone Grafts

Alveolar clefts are most commonly encountered in unilateral or bilateral cleft lip and palate patients. These defects typically result in a deformation of the alveolar arch form and hypodontia. Typically, the defect occurs at or near the maxillary lateral incisor, mesial to the canine. This bony deficiency does not allow for successful eruption of the maxillary incisors near the cleft and can result in displacement of surrounding teeth. The anatomic shape of alveolar cleft defects is a 3-dimensional (3D) trapezoid (Fig. 1).

Alveolar clefts can cause significant functional and cosmetic impairments. Clefts that are not repaired (or are inadequately repaired) may result in poor speech, difficult hygiene, nasal asymmetry with poor alar base support, non-eruption of teeth in the cleft area, and malocclusion with poor ability to correct maxillary arch collapse and unify the arch.[79] Discontinuity of the maxillary arch also increases the difficulty of a future Le Fort 1 advancement. The main objectives of alveolar cleft repair are to close the oronasal fistula, unify the maxilla, provide support for the nasal alar base, and allow for eruption of the dentition surrounding the cleft.

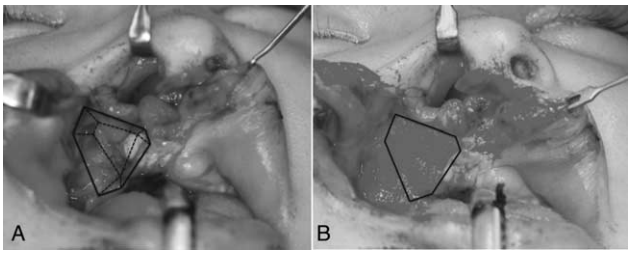

FIGURE 1. Intraoperative images of a patient with right cleft lip and palate undergoing a primary lip and nose repair and simultaneous GPP. A. The alveolar defect is represented anatomically as a 3-dimensional trapezoid shape that spans the floor of the nose superiorly, to the alveolar ridge anteriorly, to the bottom of the gingiva or adjacent tooth root with attached gingiva inferiorly, and to the incisive foramen posteriorly. B. The BMP-2 impregnated collagen gel fills the alveolar defect after closure of the deep mucosal flaps. BMP, bone morphogenetic protein; GPP, gingivoperiosteoplasty.

Gingivoperiosteoplasty (GPP) is an early soft tissue closure of an alveolar cleft at the time of the primary lip or palate repair during infancy. Historically, GPP surgery in wide alveolar defects was fraught with concerns of diminished maxillary growth. However, currently, nasoalveolar molding (NAM) therapy in the newborn cleft can align the maxillary arch and bring the greater and lesser segments in close approximation (Fig. 2). This allows for a GPP on a smaller defect. It has been shown that a GPP after NAM therapy does not lead to more diminished maxillary growth and reduces the need for secondary alveolar bone grafting from 100% to 40%.[80] Ideally, a GPP procedure after NAM would reduce the need for secondary alveolar bone grafting to zero. BMP-2 in a collagen matrix after NAM at the time of GPP may provide the necessary bone induction to eliminate the need for secondary alveolar bone grafts. However, there is still an unresolved question of maxillary growth following the use of BMP-2.

Markings for a primary alveolar repair with BMP-2 at the time of GPP may vary slightly depending on whether the repair is performed at the time of the cleft lip (3 months) or at the time of the cleft palate repair (10 months). Alveolar segments should be approximated within a few millimeters by NAM, so vertically designed flaps within the cleft are possible for closure without significant dissection. Vertical markings within the cleft separate the deep gingival flaps from the anterior gingival flaps. Deep flaps for palatal closure are marked as extensions of the nasal floor flaps. For the inferior aspect of the gingival bottom, separate triangular flaps are marked for a Z-plasty type closure. After injection of local

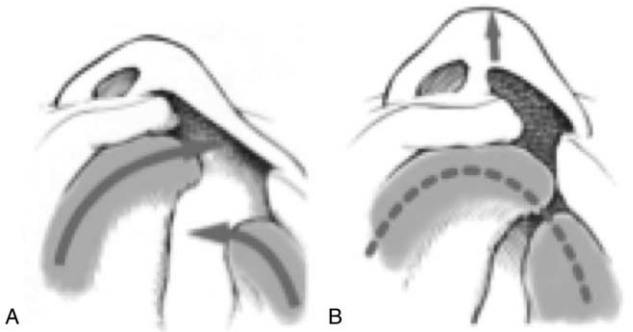

FIGURE 2. Illustration of cleft greater and lesser alveolar segments: A. Pre-NAM separation and collapse of alveolar lesser segment. B. Post-NAM alignment of arch form with narrow alveolar cleft defect in preparation for GPP and BMP-2 procedure. Also, note improvement of columellar length. BMP, bone morphogenetic protein; GPP, gingivoperiosteoplasty; NAM, naso alveolar molding.

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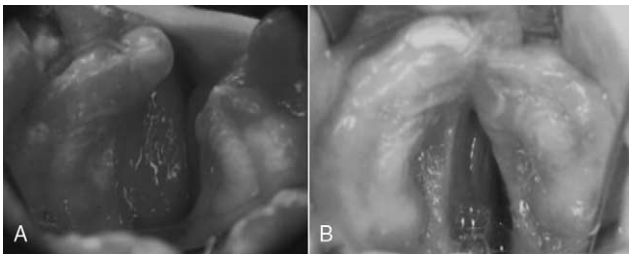

FIGURE 3. Intraoral palatal view of alveolar segments: A. Pre-NAM position of alveolar segments with wide alveolar defect. B. Postoperative view after GPP with BMP-2 and complete healing of alveolus just prior to cleft palate repair. BMP, bone morphogenetic protein; GPP, gingivoperiosteoplasty; NAM, naso alveolar molding.

anesthesia with epinephrine, a No. 15 blade or Beaver blade is used to make the gingival incisions. Limited subperiosteal dissection within the alveolar cleft is performed with a Freer elevator. Injury to tooth buds should be carefully avoided, as alveolar bone is typically very soft at this age. Nasal floor closure with anterior vomer/caudal septal flaps to the Millard's extended "L-flap" is performed with interrupted vicryl or chromic suture on a P-2 needle. Next, deep flaps are approximated. Gingival bottom flaps are transposed and sutured across the defect to the other side. The resorbable collagen matrix is impregnated with BMP-2 for 20 minutes then implanted in the defect (Fig. 1). Demineralized bone matrix may be added for support if the collagen matrix is collapsible (the implant should have enough structure to prevent soft tissue collapse in order to take advantage of "protective bone regeneration").[81] The implant is packed into the defect and on the piriform aperture for alar base support. Anterior gingival flaps are then sutured with vertical mattress 5–0 chromic or vicryl sutures so that it is watertight (Fig. 3).

Secondary alveolar cleft repair with BMP-2 is performed at mid-childhood after palatal expansion. Papillary or gingivobuccal incisions are marked extending from within the cleft to the first molar. A back-cut is planned cephalad into the buccal mucosa. Injections are performed along incisions and under flaps. A No. 15 blade is used to make the incisions and subperiosteal degloving of the maxilla and nasal region is performed with a periosteal elevator. With the maxillary mucosal flaps elevated, lateral back-cuts are made underneath the flaps in the periosteum to provide a release for a "sliding sulcus" advancement. Within the cleft, elevation of lateral cleft flap (lesser segment) and medial cleft flap (premaxilla) including a vomer flap is performed in a subperiosteal plane. Separation or bisection of flaps is sharply performed for intraoral palatal closure and nasal floor closure. Nasal floor mucosal closure is performed with interrupted Vicryl or chromic suture on a small P-2 needle. Intraoral palatal closure is performed with vertical mattress chromic sutures. Once the deep flaps are completely closed, resorbable collagen matrix impregnated with BMP-2 (with or without demineralized bone matrix) is then implanted into the alveolar cleft defect and on the piriform aperture for alar base support. Lateral gingivobuccal flaps are slid to the anterior mucosal flap for closure over the implanted graft. Dental Coe-Pak (Patterson Dental Supply, Inc., Saint Paul, MN) is placed for a dressing.

Alveolar cleft repair is currently the most common application of BMP-2 in craniofacial reconstruction. In one retrospective review of secondary alveolar cleft repair, BMP and demineralized bone matrix repaired clefts were 97% successful based on bone stock evaluated with occlusal radiographs, as compared to an 84% for clefts treated with iliac grafts.[48] Patients with iliac bone grafts also had a significantly higher rate of postoperative intraoral infections.[48] Other randomized trials have shown increased bone density and new bone formation in clefts treated with BMP constructs compared to autologous bone grafts.[50,51] Secondary alveolar bone grafts in mid-childhood are known to heal relatively well with either technique. For older patients with unrepaired alveolar clefts, outcomes are not as good. The alternative use of BMP-2 in this older patient population has been shown to improve bone healing and reduce morbidity compared with traditional iliac bone grafting.[47]

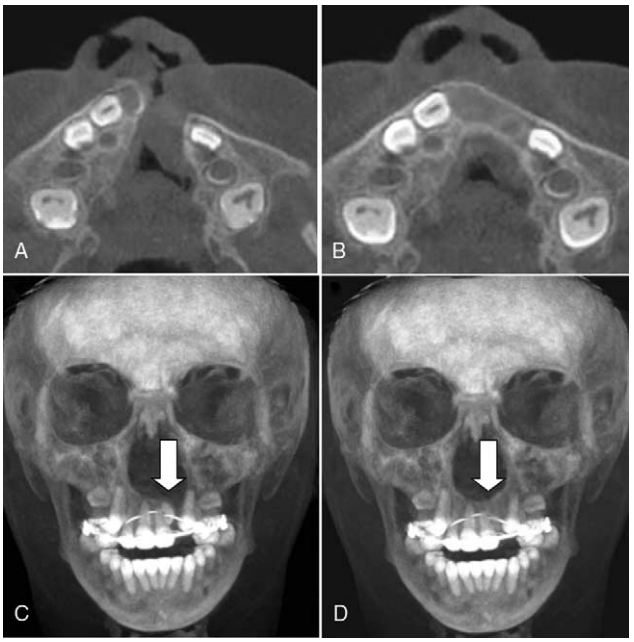

FIGURE 4. A cone beam CT scan of a patient with left cleft lip and palate. A. Preoperative axial imaging showing alveolar defect (arrow). B. Postoperative axial imaging 6 months after GPP with BMP-2 showing bone healing and mineralization across the previous bone defect. C. Preoperative frontal imaging showing left alveolar defect (arrow). D. Postoperative frontal imaging 6 months after GPP with BMP-2 showing bone healing and mineralization across the previous bone defect. CT, computed tomography; BMP, bone morphogenetic protein; GPP, gingivoperiosteoplasty.

Of note, the use of BMP has been shown to result in longer-lasting edema and more granulation tissue than autologous bone grafts.[51] Other commonly reported complications include local reactions, graft failure, infections, and other wound complications.[82–84] Other rare and/or theoretical complications include ectopic bone formation or oncologic transformation.[49,85] Complete closure with well-vascularized tissues is also important for healing and to resist exposure and infection of the implant in the perioperative period (Fig. 4).

Cranial Vault

Cranial vault defects are often the result of head trauma or prior intracranial hemorrhage necessitating decompressive craniotomy. Defects vary in size and location and have varying degrees of intervening scar from the deep dura to the more superficial periosteum, galea, or skin. Defects near the frontal sinuses or other areas lined with mucosal membranes provide an additional challenge because of the high risk of infection. Patients with large cranial defects are often required to wear protective helmets and large cranial defects may result in the "Syndrome of the Trephined," a constellation of neurologic cognitive deficits related to disruption of equilibrium of intracranial pressure.[86]

On physical exam, the edges of the bony defect are palpable, and the skin may be contracted into the depression in long-standing, large defects. This appearance has been called "sunken skin syndrome". A 3D computerized tomography (CT) scan provides

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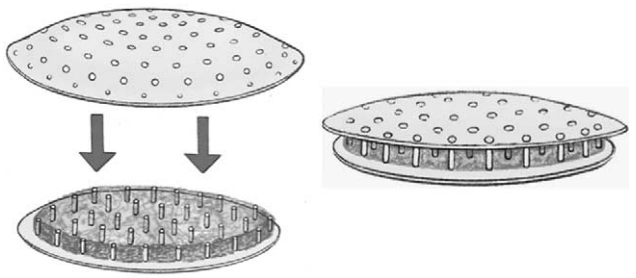

FIGURE 5. An illustration of a bilaminar construct with BMP-2 used for cranial vault reconstruction. A BMP-2 impregnated resorbable sponge is placed between 2 resorbable plates. The bottom (endocranial) plate has supportive struts, and the top (ectocranial) plate is secured with sonic welding. BMP, bone morphogenetic protein.

an accurate assessment of the defect and allows for pre-operative surgical planning.

For cranial vault reconstruction of large defects, titanium mesh plates,[87,88] custom alloplast implants (polyetheretherketone [PEEK]),[89] or autologous split calvarial bone[90] may be used to provide structural support and protect the underlying brain.[91] An alternative, and secondary option to these more commonly used techniques is the use of BMP-2 impregnated collagen sponge within a bilaminar, resorbable PLGA plate construct comprised of 50% D-lactide and 50% L-lactide (Fig. 5). The bilaminar resorbable plate with BMP-2 reconstruction will also provide similar initial structural support using resorbable PLGA support ''columns'' until bone healing occurs. In addition, like the titanium and alloplast implant, there is no donor site morbidity; like split bone reconstruction, it will result in healing of the defect with no residual foreign body.

The BMP-2 bilaminar construct can be thought of as a sandwich in which the resorbable PLGA mesh plates are the bread and the BMP-2 impregnated collagen sponge/demineralized bone matrix (DBM) is the filling. Osteoconduction may occur at the periphery and osteoinduction may occur in the center of the BMP-2 resorbable construct.

To perform BMP-2 bilaminar construct reconstruction, the incision is made considering the previous craniotomy incisions; every attempt is made to maximize the scalp blood supply. Skin flaps are raised and subperiosteal dissection around the entire cranial vault defect is performed. Along the bony borders of the defect, a small endocranial rim is developed. Power burring is performed along the osseous borders to promote osteoconductive healing. A skull model (made preoperatively from a 3D CT scan) is helpful for shaping PLGA resorbable mesh plates (Resorbex, KLS Martin, Jacksonville, FL). The endocranial plate is placed on the endocranial side of the model, trimmed, and molded with hot saline. Resorbable PLGA pins (7 mm) are placed though holes and welded to the plate as supportive columns and spacers (Fig. 6). BMP-2 is soaked onto a resorbable collagen matrix for 20 minutes, then placed with DBM around the pins. The ectocranial plate is contoured to the ectocranial surface of the model. An extra 1 cm of plate is left on the periphery to overlap the in-situ bone. This overlap of resorbable PLGA plate over the bone is used for securing with resorbable PLGA pins. The ectocranial plate is then placed on top of the pins (columns) and the collagen sponge seeded with BMP-2. This is welded together with a flat sonic weld tip to create the bilaminar sandwich. The bilaminar construct is then placed into the cranial defect, and sonic weld pins are used for fixation around the periphery. Skin flaps are closed in 2 layers over a drain placed away from the construct.

For cranial vault repair, BMP has been used in the pediatric population, where availability of split grafts are limited.[86] The addition of BMP can improve rates of defect closure when added to particulate autogenous bone graft,[49] however, an early case report demonstrated significant facial edema postoperatively that required removal of the BMP construct.[92] Overall, the use of BMP in cranial vault reconstruction is still being explored for its safety and efficacy.

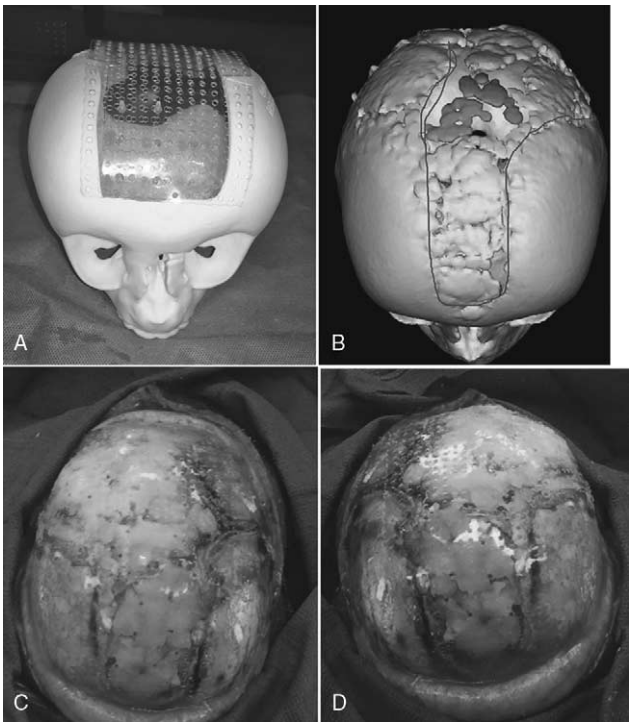

FIGURE 6. Large congenital cranial vault defect in a pediatric patient: A. CAD/CAM model used intraoperatively to fashion resorbable mesh plates for bilaminar construct. B. Three-dimensional (3D) CT scan after 6 months of bone healing. C. Intraoperative apical view with endocranial plate and BMP-2 placed. D. Intraoperative apical view with ectocranial plate placed to finish the construct. CAD/CAM, computer-aided design and computer-aided manufacturing; CT, computed tomography.

Mandibular Cribs

Mandibular defects vary widely in size and location. They can present after tumor resection or trauma, including mandibular fracture nonunion or osteomyelitis. They may be separated into anterior (symphyseal, parasymphyseal), lateral (body, ramal), or posterior (condylar) defects. The patient may report problems with mastication, oral competence, or pain. Malocclusion and soft tissue collapse can be seen on exam. Unrepaired mandibular defects can result in difficulties with mastication and speech. In addition, an ''Andy Gump'' deformity may be present, characterized by severe retrognathia and the appearance of an absent chin with contraction of the soft tissues over the area of missing bone. As with other craniofacial defects, a 3D CT scan with or without model reconstruction provides a road map for reconstructive surgery and can guide creation of customized supportive cribs.

The indication for BMP-2 crib reconstruction of mandibular defects is similar to that for a non-vascularized bone graft—defect size limit of 5 to 8 cm. In larger sized defects vascularized bone is preferred. The BMP-2 crib reconstruction is not performed after oncologic resection.

This technique of BMP-2 crib reconstruction begins with a gingivobuccal incision or Risdon incision, depending on previous incisions. Re-creation of the mandibular skeletal defect is

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performed by dissecting subperiosteally down to bone and retained hardware. Intervening soft tissue is excised. A fresh osteotomy or burring at the bony edges is performed to ensure influx of progenitor cells and osteoblasts. A titanium or resorbable PLGA crib is fashioned to outline the mandibular defect with a lingual lip and complete coverage of the inferior border and anterior border (Fig. 7). The crib is secured with either screws or resorbable PLGA pins. A resorbable collagen matrix impregnated with BMP-2 with demineralized bone matrix is packed into the crib. Meticulous closure is performed with running, locking 3–0 chromic sutures. Dental implants can be placed in select patients after osseous healing, but "Jaw in a Day" (implants at the time of free fibular reconstruction) cannot be performed using this technique.[93,94] Postoperatively, temporary placement into maxillomandibular fixation is recommended.

In a recent case series, 14 patients with mandibular critical-sized defects reconstructed with BMP-2 all had good bone healing within 5 to 6 months.[2] In a retrospective review of 17 cases of vascularized bone grafting to the mandible for osteoradionecrosis, 8 patients had BMP-2 added between the native bone and fibula flap osteotomy sites. Rates of infection and malunion were similar, and there was no increase in cancer recurrences.[95] In a randomized control trial, all patients who received BMP constructs (BMP in a resorbable collagen sponge) with a high concentration of CD34+ cells showed good mandible regeneration with high bone density.[56] As with other craniofacial uses of BMP, more studies will be useful in exploring its efficacy.

Rare Craniofacial Clefts

Tessier's rare craniofacial cleft classifications are soft and hard tissue separations based on defined embryologic zones, numbered from 0 to 14.[96] Facial skeletal defects may extend from intraoral, through the maxillary sinus, and into the orbit. Most primary rare

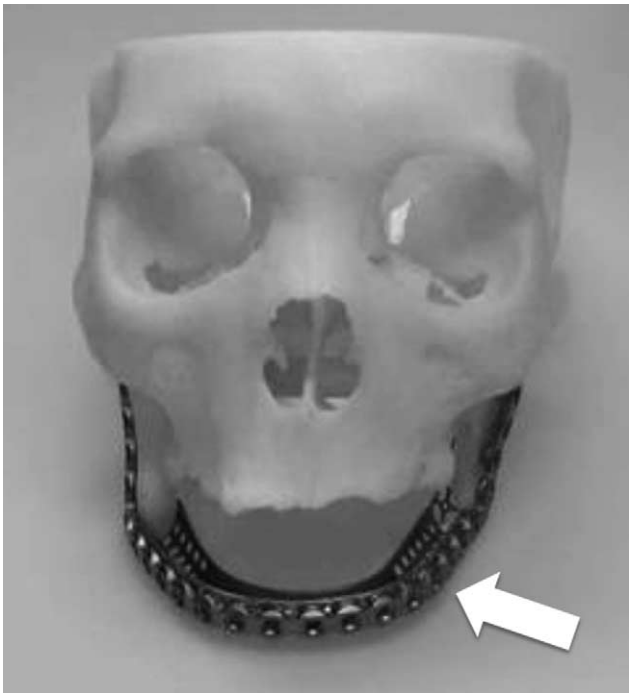

FIGURE 7. CAD/CAM model used for mandibular crib reconstruction of segmental mandibular defect. BMP-2 with demineralized bone matrix is placed within the crib for reconstruction. BMP, BMP, bone morphogenetic protein; CAD/CAM, computer-aided design and computer-aided manufacturing.

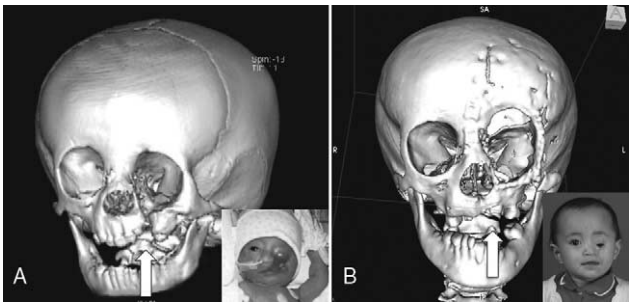

FIGURE 8. 3D CT scans of a patient with left Tessier #4 orbitofacial cleft. A. CT imaging at birth showing the osseous defect (arrow) and communication of the orbit with the maxillary sinus and the oral cavity. B. Postoperative imaging after primary repair using a BMP-2 implant showing bone healing of the maxilla and alveolus (arrow). BMP, bone morphogenetic protein; CT, computed tomography.

Tessier craniofacial cleft repairs are focused on soft tissue rearrangement; however hard tissue reconstruction should not be overlooked. Lack of skeletal support will result in soft tissue collapse and progressive increase in deformity over time. A 3D CT scan is of paramount importance because unique skeletal abnormalities may exist that the soft tissue findings only partially suggest.

At the time of soft tissue repair, complete subperiosteal dissection of the cleft may be performed which gives exposure to the bony defect. Since autologous bone donor sites may be limited in young patients, the use of BMP-2 becomes an option. An example of this BMP-2 reconstruction is a #3 or #4 rare facial cleft with ocular-sinus-oral communication (Fig. 8).

For the soft tissue flap designs, natural facial aesthetic lines should be respected. Flaps such as nasal rotation flaps, eyelid switch flaps, and lateral cheek advancement flaps are designed (Fig. 9). After injection and incisions, thick flaps are raised to ensure an adequate blood supply. Skeletal defects are completely dissected, intervening soft tissue excised, and deep flaps are raised for mucosal closure. After closure of deep flaps, BMP-2 in a collagen matrix, combined with DBM, is implanted into the skeletal defect. Anterior flaps are rotated, transposed and closed in layers with resorbable sutures. Because of their rare nature, randomized studies have not been performed on the use of BMP-2 constructs in Tessier cleft

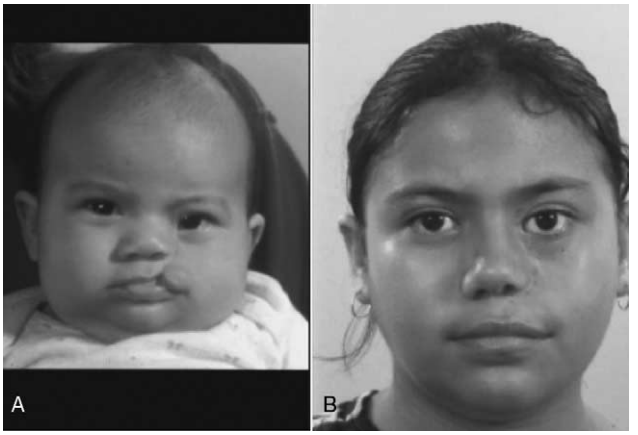

FIGURE 9. Patient with left #4 orbitofacial cleft demonstrating soft tissue flap closure. A. Infant image with incomplete cleft prior to procedure. B. Patient at skeletal maturity many years after soft tissue repair of #4 cleft with flaps within facial aesthetic lines used for nasal rotation, eyelid switch flaps, and lateral cheek advancement.

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repair. Unlike alloplastic implants, reconstructions utilizing resorbable materials and BMP-2 will continue to grow with the developing craniofacial skeleton (after absorption of PLGA plates). Secondary procedures during mid-childhood and at skeletal maturity for patients with rare craniofacial clefts are often required and may include scar revisions, additional bone grafting, or maxillary orthognathic procedures.

DISCUSSION

Outcome studies on the use of BMP-2 in craniofacial reconstruction are defining appropriate indications and uses. Currently, BMP remains outside the scope of standard of care in craniofacial reconstruction. Challenges include side effects, cost, and a paucity of long-term data. However, BMP-2 is a powerful tool that may be the only answer in difficult reconstructions.

Like many innovations, BMP-2 is not a panacea but is a useful tool for specific indications. Multiple recent advances in craniofacial surgery may complement its use and improve its side effect profile. For example, custom manufactured carriers based on a patient's unique CT scan can be designed to perfectly fill the bony defect, thus delivering BMP accurately and with minimal effect on surrounding tissue. In addition, current work is being performed to decrease local inflammation cause by BMP-2 by suppressing pro-inflammatory cytokines.[97] These advances may ultimately improve the side effect profile of BMP-2 and expand its use.

CONCLUSIONS

We focused on 4 craniofacial operative procedures that may benefit from BMP-2 including alveolar cleft repair (both primary and secondary), cranial vault defect reconstruction, mandibular skeletal defect reconstruction (with supportive crib), and rare Tessier cleft osseous repair. We documented operative techniques and indication. Future directions of BMP-2 therapies will become apparent as prospective randomized trials report outcome data.

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