Reconstruction of 10 Major Mandibular Defects Using Bioimplants Containing BMP-7

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ABSTRACT

Purpose: The limitations and morbidity associated with autogenous bone grafting have driven the search for predictable bone substitutes and bioimplants. A novel method of reconstruction was tested in this case series.

Materials and Methods: Ten patients with major mandibular defects following resection of biopsy-proven ameloblastoma lesions or osteomyelitis of the mandibular body or ramus were included in this study. The resection defects were spanned with rigid reconstruction plates to hold the remaining mandibular segments in the correct position. The defects were filled with a bioimplant containing bone morphogenetic protein-7 (BMP-7) in a demineralized bone matrix (DBM) suspended in a reverse-phase medium to effect sustained BMP delivery.

Results: The postoperative course for all 10 patients was uneventful. Radiographic evidence of mandibular bone formation was found in all cases. At the end of 1 year, functional and esthetic reconstruction of the mandible was complete.

Conclusion: Bioimplants containing BMP-7 in DBM suspended in a reverse phase medium were successful in restoring major mandibular defects in nonirradiated beds in this series of 10 patients.

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Autogenous bone grafting is considered to be the gold standard for repair of most osseous defects,[1,2] including those in the maxillofacial region. However, there are limits to the amount of bone that can be harvested from a patient's skeleton. Autogenous bone grafts may also increase the risk of morbidity — such as infection, pain and length of hospital stay — associated with the second harvest site.[3,4] As a result, there has been recent interest in the development of new grafting materials using allogeneic, xenogeneic and synthetic bioimplants for reconstructive bony procedures. Numerous studies have compared the effectiveness of these alternatives as potential replacements for autogenous bone grafts.[5–9]

Allogeneic bone, such as demineralized bone matrix (DBM), harvested from one individual and transferred to another of the same species was first used to reconstruct skull defects in dogs more than 100 years ago.[10,11] It was not until Dr. Marshall Urist, a University of California clinical-scientist, reported the results of years of research in his 1965 landmark article that researchers and clinicians seriously considered demineralized allogeneic bone as a potential bioimplant for osseous repair.[12,13] However, because allogeneic bone is harvested from an individual other than the patient, concerns exist about the potential for disease transmission. As a result, allogeneic bone is less than ideal as a grafting material.

Table 1 Mandibular defects reconstructed using a combination of BMP-7 and DBM putty

Patient's age (years)	Sex	Description of lesion	Size of lesion (cm)	Site of resection	IA nerve
40	Male	Ameloblastoma	9	Ramus and body of the mandible	Spared
44	Female	Ameloblastoma	5	Body of the mandible	Resected
55	Female	Ameloblastoma	3	Body of the mandible	Resected
18	Male	Ameloblastoma	3	Ramus of the mandible	Spared
61	Female	Ameloblastoma	7	Ramus and body of the mandible	Resected
37	Female	Ameloblastoma	6	Anterior mandible	N/A
53	Male	Osteomyelitis	5	Body of the mandible	Spared
28	Female	Ameloblastoma	5	Body of the mandible	Spared
73	Male	Ameloblastoma	5	Body of the mandible	Spared
22	Female	Ameloblastoma	7	Ramus and body of the mandible	Resected

BMP-7 = bone morphogenetic protein-7; DBM = demineralized bone matrix; IA nerve = inferior alveolar nerve; N/A = not applicable.

Bone Morphogenetic Protein

With the constraints associated with both autogenous and allogeneic bone, scientists began to focus on the fabrication of completely synthetic bioimplants. By the late 1980s, the active factor responsible for the induction of bone was identified: bone morphogenetic protein (BMP). BMP replicates the embryonic induction of bone formation.[14] It can induce pluripotent mesenchymal stem cells to differentiate into bone-forming osteoblasts. BMP-2, -4 and -7 have been shown to stimulate de novo, in vitro and in vivo bone formation in various animal models. Many other BMPs have been isolated and, with the exception of BMP-1, they are all members of the transforming growth factor β (TGF-β) superfamily.[15] In the early 1990s, it became possible to fabricate these proteins synthetically using recombinant technology and, by 2006, this finally led to the development of OP-1 (BMP-7; Stryker Biotech, Hopkinton, Mass.) and Infuse (BMP-2; Medtronic, Fridley, Minn.), both of which are now available for clinical use.[16]

One of the greatest challenges in the clinical application of BMP has been the identification of an acceptable carrier. Investigation of various delivery agents has identified those that are more effective for the optimal clinical application of BMP.[17–21] Over the past decade, our group has explored the use of a reverse-phase medium as a carrier for BMP. While others have struggled to achieve acceptable clinical results, we achieved our first successful BMP bioimplant in 1999.[22] Since then, we have reconstructed 10 human mandibular defects using bioimplants consisting of OP-1 (BMP-7) and DynaGraft Putty (DBM in a reverse-phase medium; IsoTis, Irvine, Calif.). In this article, we describe the technique used to reconstruct major mandibular defects in these patients, explore the outcomes and discuss future directions.

Materials and Methods

All 10 patients in our case series were diagnosed with a biopsy-proven ameloblastoma or osteomyelitis in the body or ramus of their mandible (**Table 1**). There were 6 females and 4 males. Ages ranged from 18 to 73 years with a mean of 43.1 years. In 3 of the patients, an intraoral approach was used to gain access to the lesion. For these patients, the inferior alveolar nerve was preserved intact by carefully dissecting it from the mandible before the lesion was excised and the peripheral resection was performed, preserving the inferior border of the mandible. For the remaining 7 patients, a traditional extraoral submandibular approach was used to expose the body and ramus of the mandible (**Figs. 1a–d**). A 2.4-mm locking reconstruction plate (Biomet Microfixation Inc., Jacksonville, Fla.) was adapted to the affected hemimandible (**Figs. 2a, b**), ensuring that at least 3 fixation holes were available at each end of the lesion to attach the plate. The lesion was then carefully excised from the mandible ensuring that margins of at least 1 cm of normal tissue were achieved. This was confirmed by examining postoperative frozen sections of the bone marrow and adjacent soft tissue.

In all cases, the BMP bioimplant was created by manually mixing BMP-7 (OP-1) with 10 mL of DBM in a reverse-phase medium (DynaGraft Putty), then molding it to the shape of the resected segment of mandible (**Figs. 3a–d**). The implant was inserted into the mandibular defect and the muscular sling surrounding the mandible was re-approximated to ensure complete coverage of the bioimplant (**Figs. 4a–d**). The superficial tissues were then closed in a traditional fashion. Patients were carefully followed, both clinically and radiographically, to ensure proper integration of the bioimplant with the mandible.

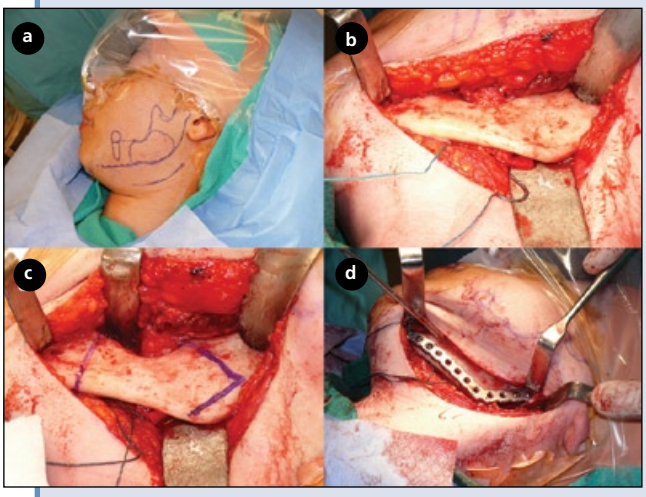

Figure 1: (a) Left lateral facial view of the patient prepared for the surgical procedure. The outline of the mandible including the lesion is marked on the patient's cheek. The proposed incision is outlined immediately below the inferior border of the mandible. **(b)** Using the submandibular approach, the entire left hemimandible is exposed. **(c)** A surgical marker is used to identify the proposed mandibular resection margins. **(d)** The mandibular reconstruction plate is adapted to the left lateral aspect of the mandible before mandibular resection.

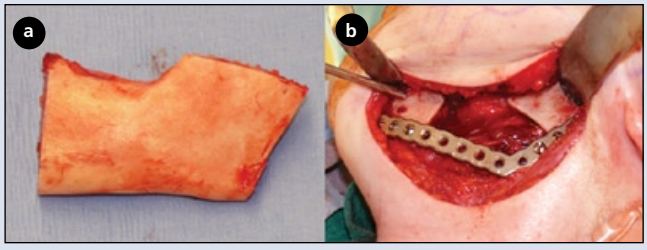

Figure 2: (a) The resected aspect of the left mandibular body and mandible containing the lesion. **(b)** The resultant mandibular defect following resection of the lesion. The reconstruction plate restores the posterior and inferior border of the mandible.

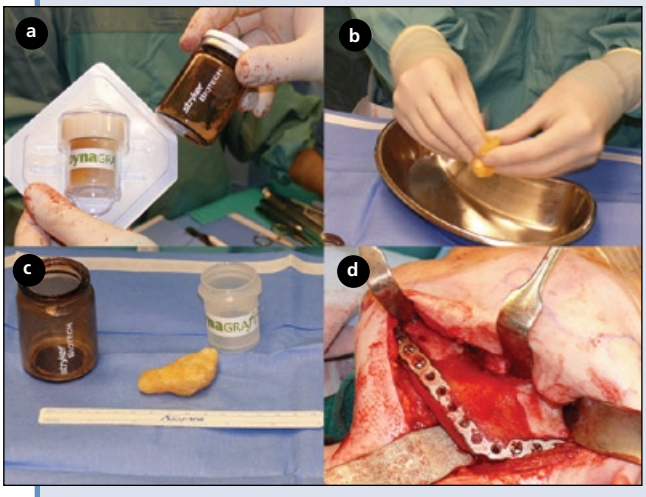

Figure 3: (a) The 2 commercially available materials required to fabricate the bone morphogenetic protein (BMP) bioimplant. **(b)** The 2 products are manually mixed to create the BMP bioimplant. **(c) T**he BMP bioimplant is molded to the form of the mandibular defect. **(d)** The mandibular defect reconstructed with the BMP bioimplant.

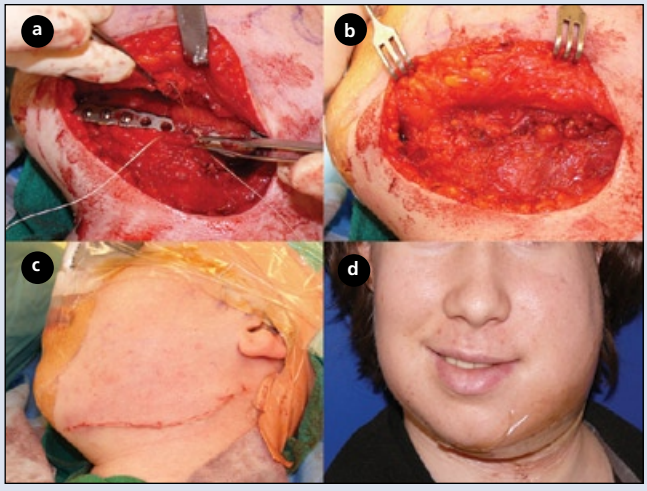

Figure 4: (a) The muscular sling, rich in satellite stem cells, is carefully re-approximated around the BMP bioimplant. **(b)** The muscular sling completely encompasses the bioimplant. **(c)** The incision is closed to restore the form of the lateral face. **(d)** One week after surgery, swelling on the left lateral face is indurated and, for patients receiving BMP bioimplants, does not resolve for > 4 weeks postoperatively.

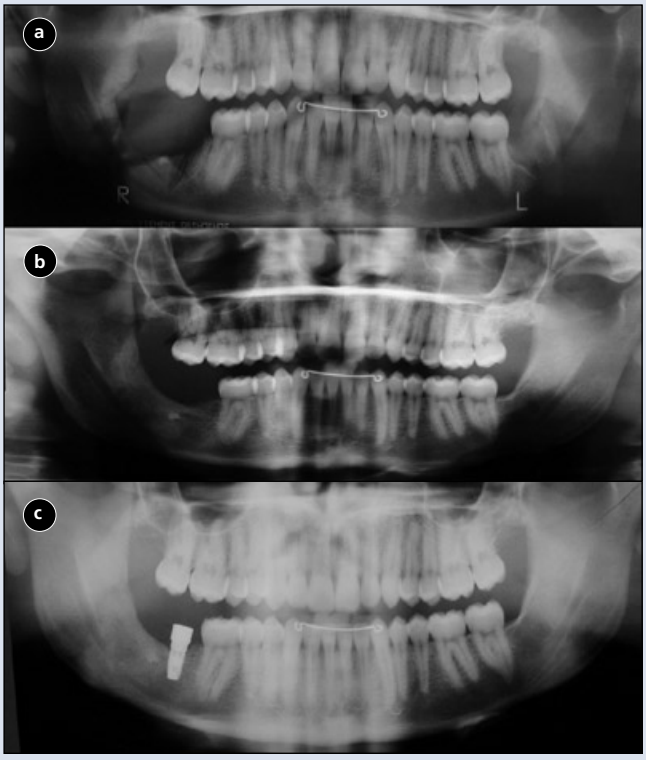

Figure 5: (a) Panoramic radiograph demonstrating a defect in the right posterior mandible of a 19-year-old man whose ameloblastoma was removed using an intraoral approach in the right retromolar region. **(b)** A year after reconstruction of the right posterior mandible using a BMP bioimplant, complete restoration of the region of the defect is seen. **(c)** Four months following placement of a dental implant into a reconstructed region of the right posterior mandible, the implant has successfully integrated into the newly regenerated bone.

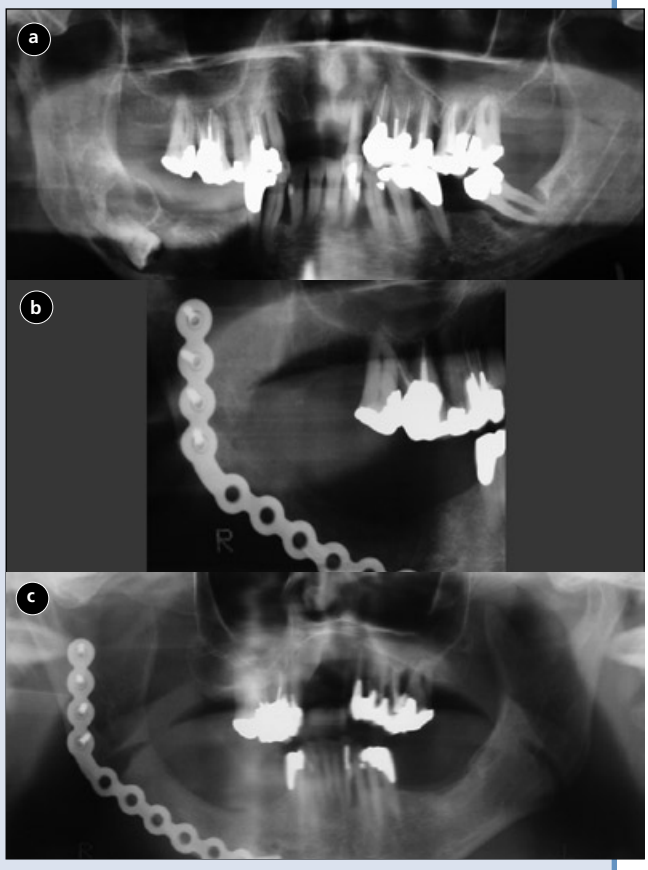

Figure 6: (a) Panoramic radiograph of a 62-year-old man demonstrating an impacted tooth 48 with an associated multilocular, radiolucent lesion (ameloblastoma). **(b)** Panoramic radiograph 9 months following mandibular resection and reconstruction with a BMP bioimplant shows limited evidence of bone formation. **(c)** One year following reconstruction of the mandibular defect, this panorex revealed complete regeneration of the mandible.

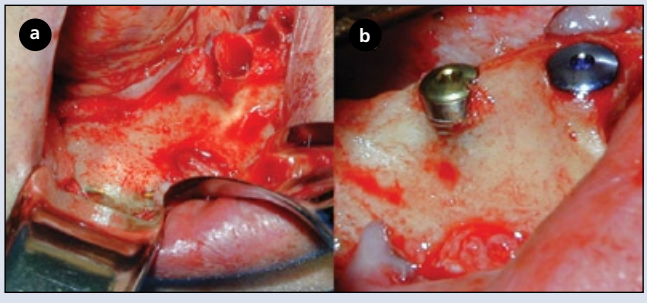

Figure 7: (a) During dental implant placement, BMP-regenerated bone was exposed distal to the mental nerve. It was difficult to differentiate between newly regenerated bone and unresected bone anterior to the mental nerve. **(b)** A dental implant placed into bone that was regenerated by the BMP bioimplant.

Results

All patients were followed for a minimum of 9 months and all have demonstrated clinical and radiographic evidence of restoration of mandibular continuity (**Figs. 5a–c** and **6a**) with no complications. Of the 10 patients, 4 have had dental implants placed in their reconstructed mandibles (**Figs. 5a–c**). In 1 case, the implants were placed 8 years following the reconstructive surgery. It is important to note that, in all 10 patients, bone formation was consistently first appreciated on clinical examination during manual manipulation of the reconstructed segment; radiographic evidence of bone formation was not fully evident until 1 year after the reconstructive procedure (**Figs. 6b** and **6c**). However, at 1 year following reconstruction, it was difficult to differentiate between bone that was formed from the BMP bioimplant and native preexisting bone (**Figs. 7a, b**).

Discussion

Successful reconstruction of large mandibular defects must ensure the restoration of mandibular height and width, which are essential for functional prosthetic rehabilitation. Proper reconstruction will also ensure that appropriate facial form is recreated. For the patients presented in this case series, we were able to meet these objectives. Just as important, patient morbidity and overall cost to the health care system, including length of hospital stay, were significantly reduced.

Although autogenous bone grafting remains the "gold standard" for these clinical scenarios, it has several limitations. Because the number of donor sites available in the human skeleton is limited, only a finite quantity of bone can be harvested.[3] Furthermore, the surgical morbidity (8%–10%), including pain, paresthesia, anesthesia and infection, associated with autogenous bone harvesting may be greater than that experienced at the primary surgical site. In addition, the quality of harvested bone may also vary depending on the patient and the site of procurement.[23]

The synthetic bone used for these patients overcomes the problems associated with autogenous bone grafting. Ideally, a bone substitute should mimic the healing of autogenous bone and ultimately be resorbed and completely replaced by host bone. This was seen with the BMP bioimplants presented in this case series. Successful reconstruction of 10 major mandibular defects was achieved using a BMP bioimplant consisting of recombinant BMP-7 delivered by DBM suspended in a reverse-phase medium. Both functional and esthetic results were comparable if not superior to those achieved with autogenous bone grafting. In addition, the procedure saved health care system costs as a result of decreased operating room time and length of hospital stay.

The future of bone reconstruction for oral and maxillofacial rehabilitation has significantly advanced over the past decade with our improved understanding of bone healing and the discovery of growth-inducing factors, such as BMP. As we develop technologies that will facilitate the delivery of these agents, making them more clinically manageable and cost effective, we expect them to have a significant impact on the future of reconstructive dentistry.

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