Bone Morphogenetic Protein for Sinus Augmentation

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Bone morphogenic proteins (BMP) are members of the family of transforming growth factors. Fifteen different BMP have been identified, all with varying degrees of cellular activity, including cartilage- or bone-inductive properties. Two recombinant proteins are available: recombinant human bone morphogenetic protein (rhBMP)-2 and rhBMP-7. These products have been investigated as alternatives to autogenous bone grafts in a variety of clinical situations, including spinal fusions, fracture repair, treatment of bone defects, and reconstruction of maxillofacial conditions. Reconstruction in the maxillofacial region includes alveolar ridge augmentation, mandibular reconstruction, and maxillary sinus augmentation.

Recombinant bone morphogenic protein administration

The BMP product is packaged as a lyophilized powder in a sterile vial. At the time of surgery, the powder is reconstituted with sterile water and applied to the carrier. rhBMP-2 or rhBMP-7 is delivered to the bone grafting site in a carrier material. Carrier systems, which are absorbed over time, maintain the concentration of the rhBMP at the treatment site, provide temporary scaffolding for osteogenesis, and prevent extraneous bone formation by bonding the BMP to the carrier material. Carrier systems have included inorganic material, synthetic polymer, natural polymers, and bone allograft. The current collagen sponge carrier does not have significant mechanical strength to maintain a specific form. For interbody spinal fusion, the BMP delivery system is an interbody fusion cage.

Two rhBMP-associated carrier/delivery systems have received approval from the US Food and Drug Administration. Osteogenic protein-1 (OP-1) consists of rhBMP-7 and bovine collagen (Stryker Biotech Hopkinton, Massachusetts), which is reconstituted with saline to form a paste. The addition of carboxymethylcellulose forms a putty. The InFuse system (Medtronic Sofamor Danek Warsaw, Indiana) consists of rhBMP-2 on an absorbable bovine type I collagen sponge carrier. The labeled indications (as of May 2005) for these devices are summarized below:

- OP-1 Implant is indicated for use as an alternative to autograft in recalcitrant long bone nonunions where the use of autograft is unfeasible and alternative treatments have failed.
- OP-1 Putty is indicated for use as an alternative to autograft in compromised patients requiring revision posterolateral (intertransverse) lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion.
- In conjunction with an LT-cage lumbar tapered fusion for spinal procedures in skeletally mature patients who have degenerative disk disease at one level from L4 to S1 (ie, labeled indication for InFuse)

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For the treatment of acute, open fracture of the tibial shaft (ie, labeled indication for InFuse)

The use of BMP is considered investigational for all other indications, including the following:

- As an alternative to autograft in compromised patients requiring revision posterolateral intertransverse lumbar spinal fusion, for whom autologous bone and bone marrow harvest are not feasible or are not expected to promote fusion (ie, labeled indication for OP-1)
- Treatment of spinal fusion or spinal fusion in the thoracic or cervical vertebrae
- As an alternative or adjunct to bone grafting in other locations, including craniomaxillofacial surgeries

rhBMP-2 and rhBMP-7 are contraindicated for patients who have known hypersensitivity to rhBMP-2 or -7 or to components of the formulation. These proteins are not recommended for use in the vicinity of a resected or existent tumor, in patients who have active malignancy or
patients undergoing treatment for a malignancy, in patients who are skeletally immature, in pregnant women, or in patients who have an active infection at the operative site.

Antibody formation to rhBMP-2 or its influence on fetal development has not been assessed. The safety and effectiveness of this device has not been established in nursing mothers. Women of child-bearing potential should be advised to not become pregnant for 1 year after treatment with this device.

Literature review

There are a limited number of studies involving maxillary sinus augmentation using BMP. Boyne and colleagues were one of the first groups to augment the maxillary sinus with
Fig. 3. (A) This 65-year-old woman was treatment planned for sinus grafting in preparation for implant placement and a fixed restoration in the posterior right maxilla. The sinus membrane was elevated with the patient under local anesthesia. (B) The BMP-impregnated collagen membrane was placed into this normal-sized sinus. BMP (12 mg) was used in this sinus. No membranes were used to cover the sinus graft site. (C) Six months later, three implants were placed. Note the excellent bone formation over the previously made window. (D) Immediate post-restoration panoramic radiograph showing bone formation at the apical portion of the implants. (E) Three-year post-restoration photograph demonstrating excellent soft tissue reaction to the implants. (F) Three-year post-restoration radiograph of the implants showing dense bone formation in the grafted sites. (G) Preoperative reformatted CT scan in area to be grafted with BMP. (H) Six-month post-BMP grafted sinus showing bone formation.
rhBMP-2/ACS in humans. Twelve patients underwent maxillary sinus augmentation, with total delivery doses of implanted rhBMP-2 (Genetics Institute, Cambridge, MA) varying from 1.77 to 3.4 mg (mean 2.89 mg) per patient. Significant bone growth was documented by CT. The overall mean height response for the maxillary sinus floor augmentation was 8.51 mm after 16 weeks (95% confidence interval 6.07–10.95). The most frequent adverse effects were facial edema, oral erythema, pain, and rhinitis. Of the 11 patients, eight had adequate bone for placement of dental implants of the desired size after 6 months of healing. However, 11 of the 12 patients received dental implants without additional bone-grafting procedures. Core biopsies obtained at the time of dental implants revealed moderate to large amounts of osseous trabecular bone. Several other studies have been published in nonhumans.

Hanisch and colleagues performed sinus augmentation in four cynomolgus monkeys using rhBMP-2 (0.19 mg per implant)/ACS. The study provided evidence for considerable vertical bone gain in the subantral space after surgical implantation of rhBMP-2. The newly formed bone in rhBMP-2 and control sites exhibited a trabecular pattern indistinguishable from
residual bone. Polarized light microscopy suggested that the new bone was predominantly lamellar. Bone implant contact to the titanium implants was similar in newly formed bone and residual bone. There was a statistically significant difference in mean vertical bone gain between rhBMP-2 (6.0 ± 0.3 mm) and control sites (2.6 ± 0.3 mm; \( P < .002 \)). Cancellous bone density within newly formed bone averaged 14.4 ± 2.9% and 13.9 ± 4.6% for rhBMP-2 and control sites, respectively, with no significant differences.

Maxillary sinus augmentation comparing rhBMP-2/ACS (12.5 μg) with iliac crest particulate cancellous bone (control group) with subsequent dental implant placement was performed in 30 rabbits. After 12 weeks of subantral augmentation, titanium dental implants were placed and allowed to osseointegrate for 3 months. There was comparable histologic and histometric evidence of bone formation between both groups. The mean vertical bone gain was significantly greater in rhBMP-2 sites than in control sites \( (P < .002) \). Bone density and bone–implant contact between the rhBMP-2 and the control group were similar. The rhBMP-2–induced bone seems to be of similar quality and as suitable for osseointegration as the residual bone.

Roldan and colleagues evaluated the benefit of platelet-rich plasma (PRP) in sinus grafting compared with rhBMP-7 using anorganic bovine bone as an osteoconductive medium in five miniature pigs. In this experiment, 420 μl rhBMP-7 was used. The mean bone–implant contact using rhBMP-7 was 45.8% and was 5.7% under PRP \( (P = .002) \). The mean height of newly mineralized bone in the augmented area using rhBMP-7 was 8.3 mm and was 3.6 mm under PRP \( (P = .013) \). rhBMP-7 led to superior outcomes with regard to the osseointegration of dental implants and the height of new bone as compared with the use of PRP. Terheyden and colleagues performed a similar study and reported comparable results. Margolin and colleagues evaluated the healing response and bone formation stimulated by three doses of recombinant human OP-1 (rhOP-1) of 0.25, 0.6, and 2.5 mg OP-1 per gram of collagen matrix, natural bone mineral, or collagen matrix alone (control) placed in the maxillary sinus of adult chimpanzees. Sinus augmentation with natural bone mineral or 2.5 mg OP-1 per gram of collagen matrix induced comparable radiographic and histologic evidence of bone formation. McAllister and colleagues showed that 2.5 mg OP-1 per gram effectively stimulates bone formation in the maxillary sinus in chimpanzees. Van den Bergh and colleagues looked at three patients (total five sinus sites) and performed 2.5 mg of rhOP-1 and collagen carrier versus autogenous iliac crest bone grafts. One patient’s core biopsy showed mature lamellar type of bone. In the second patient, no bone was found. The third patient had bilateral maxillary sinus augmentation (histologically similar to normal bone) and had successful implant integration.

### Technique

The technique described in this article is that for BMP2 applied to a resorbable collagen sponge. Sinus grafts with recombinant BMP-2 are performed in a similar manner as other sinus graft procedures (Figs. 1–4). However, the data available are for the use of BMP placed through a lateral maxillary wall window and not through an intra-alveolar "socket" approach.

After the infiltration of local anesthetic (typically 1% or 2% Xylocaine with 1:100,000 epinephrine to the maxilla and vestibule), a crestal incision is made combined with appropriate vertical release to allow for a full-thickness, subperiosteal elevation to expose the lateral wall of the maxilla. A round bur is used to create the outline of the window, and the sinus membrane is elevated carefully to avoid or minimize membrane tears. Preservation of the lateral wall of the maxilla or maintaining it as the roof of the sinus floor graft is based on clinician preference. This surgical team does not obdurate membrane tears with membranes.

The BMP is supplied as a lyophilize powder in a vial. Based on the size of the BMP to be used, the manufacturer’s recommendations are followed meticulously to reconstitute the BMP powder into solution. The resultant solution containing BMP is transferred to a sterile syringe and applied to the collagen sponge (Fig. 2C, D).

In an organized manner, liquid drops are applied to the sponge to equally distribute the BMP to the sponge. The entire BMP liquid is placed onto the sponge. At least 15 minutes are allowed for the BMP in solution to bind to the collagen sponge. After 15 minutes has elapsed, the sponge is cut into strips approximately 15 mm in width. The sponge strips are placed into the sinus.
between the bony floor and the elevated membrane (Figs. 1D, 2E, 3B, 4D). After the sinus has received the sponge, the incisions are closed with appropriate suture, typically silk or chromic. Postoperative instructions are similar as with any sinus graft. The patient should avoid Valsalva maneuvers, such as blowing the nose. Antibiotics are administered for 1 week.

Serial panoramic radiographs are not necessary to evaluate bone formation. A 4-month postoperative panoramic radiograph shows bone formation in preparation for implant placement 6 months after graft placement.

When placing implants into a sinus grafted with BMP, the bone may feel soft or hard, depending on the density of bone that was formed by the patient. We allow 4 to 6 months for implant integration based on the density of bone felt at the time of implant placement.

Further readings


