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Use of BMP in small animal orthopedics

Randy J. Boudrieau DVM, Diplomate ACVS, Professor of Surgery
Cummings School of Veterinary Medicine at Tufts University, N. Grafton, Massachusetts, USA

The “gold standard” for augmenting bone healing in humans and animals remains the autogenous cancellous bone graft. Approximately 1.5 million bone-grafting procedures are performed on humans annually in the United States; the number performed in companion animals is unknown, but likely substantial. Unfortunately, bone grafts have a number of potential drawbacks. These include an increased anesthetic time for graft harvesting, insufficient quantity of graft—either limited access to donor sites, loss of osteogenic cells, donor site pain or hemorrhage, and predisposition of the donor bone to failure.

In 1965 Marshall Urist discovered that the extracellular matrix of allogeneic bone contained a previously unrecognized substance that elicited new bone formation when implanted extraskeletally (heterotopically) in rodents and rabbits. The sequence of events he documented over a 4 week period was reminiscent of embryonic bone development and postnatal endochondral ossification: Undifferentiated mesenchymal cells migrated to the implantation site (chemotaxis) where they multiplied (mitosis) before differentiating into cartilage cells. A cartilaginous matrix was laid down and subsequently replaced with newly formed bone. The latter then remodeled to form an ossicle possessing a central marrow core. Urist later (1971) introduced the term bone morphogenetic protein (BMP) to describe the substances responsible for these phenomena. The osteoinductive properties of endogenous BMPs derived from the bones of numerous mammalian species including rats, rabbits, pigs, sheep, cattle, reindeer, moose, primates, and humans have since been characterized.

Bone morphogenetic proteins (BMPs) are differentiative factors with a principal function of inducing transformation of undifferentiated mesenchymal cells into chondroblasts and osteoblasts in a dose-dependent manner. Purification of endogenous BMPs, however, is a very complex and time consuming process. Fortunately, recombinant DNA technology, employing mammalian (e.g., hamster) and bacterial (e.g., E. coli) cell lines, now allows their production in large and highly purified quantities. As many as 15 recombinant human BMPs (rhBMPs) have been identified. Their osteoinductive ability has been tested at a number of carriers have been used to deliver both the endogenous and recombinant BMPs to the area desired. They function to slow degradation and/or diffusion of the rhBMPs from the implant site, prevent prolapse of soft tissues into the implant site, and serve as an osteoconductive medium for subsequent bone deposition. Perfecting carrier properties remains an ongoing process.

At present, the most widely used carrier is the absorbable collagen sponge (ACS), largely because of its excellent safety record and pre-existing approval for use as hemostatic agents and wound coverings. The proteins differentially bind to the sponges as a function of their isoelectric point. RhBMP-2 and -7 have been approved for clinical use as alternatives to bone grafts. Bovine type I tendon-derived ACS is currently the approved carrier for commercially available rhBMP-2 products (INFUSE® Bone Graft and Inductos®, Wyeth, Cambridge, MA). The marketed rhBMP-7 products also use collagen carriers: One is a particulate bovine bone-derived type I collagen matrix (OP-1® Implant, Stryker Biotech, Hopkinton, MA) and the other is a particulate collagen matrix combined with carboxymethylcellulose (OP-1® Putty, Stryker Biotech, Hopkinton, MA).

Recently, injectable calcium phosphate cements (CPCs) that set under endothermic conditions to form poorly crystalline hydroxyapatite have been the subject of investigation. The low endothermic setting eliminates thermal damage to the proteins, the calcium phosphate chemistry enhances protein binding, and the poor crystallinity of the material enhances its resorption, thereby minimizing interference with bone healing. This composite has been shown to accelerate healing of osteotomies in rabbits, dogs, and non-human primates. This carrier, however, has not yet been approved for human clinical use.

The osteoinductive response to BMPs is dose dependent regardless of the method of application. The osteoinductive response also is inversely proportional to the species’ position on the phylogenetic scale. The quantity of rhBMPs needed clinically for osteoinduction, however, is many times that of the corresponding endogenous BMP derived locally or from implantation of autogenous bone graft. The osteoinductive response also is dependent upon the delivery vehicle, which affects the retention characteristics of local BMP. A number of research models have utilized animals in preclinical studies that demonstrated accelerated recovery of biomechanical strength and radiographic union using rhBMP-2 and rhBMP-7 in rabbit, dog, goat, and non-human primate spontaneously healing osteotomy models. Prior to approval of this drug in the USA, Europe and Canada, their efficacy has been demonstrated in controlled human studies (acute tibial fractures repaired with IM nails, and nonunions).

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The clinical experience in veterinary medicine has been very limited to this point in time. Nevertheless, the extensive preclinical testing has provided a large amount of data for our potential clinical use in veterinary patient. Our own clinical experience in small animals has been limited primarily to the bovine type I tendon-derived ACS as the carrier; however, we also have some experience with the CPCs.

**CLINICAL REPORTS OF BMP IN THE VETERINARY LITERATURE**

The first published report of BMP use (Paatsama, 1996) was using purified endogenous BMP delivered in a coral and tricalcium phosphate carrier for repair of delayed and nonunions, and to fill the defects left following after osteotomy, all of which were performed in dogs. There also are two case reports of successful fusion of a femoral and radial/ulnar nonunion in the dog using BMP (Itoh, 1998 and Hyeok, 2001). Schmoekel (2004) has reported the use of a recombinant non-glycosylated BMP-2 (nglBMP-2) delivered in a fibrin matrix, in combination with standard fixation techniques, for intercarpal fusion in 10 canine clinical patients. Schmoekel (2004) also has reported the use of nglBMP-2/fibrin composite for the treatment of 8 long-bone nonunions in 5 cats and 3 dogs. An rhBMP-2 - collagen sponge - tricalcium phosphate (TCP) composite matrix was successfully used to successfully correct severe mandibular malocclusion and bridge a large gap in a 14 month old Golden Retriever (Boudrieau, 2004). An occipitocervical fusion was reported (Boudrieau, 2006) to have been successfully performed dorsally using rhBMP2 - collagen sponge - TCP composite matrix, in conjunction with locked plating stabilization in an 8 month old Border collie with a severe congenital malformation and malalignment of the cervical spine.

**ADDITIONAL CLINICAL USAGE OF BMP (RJB)**

The following cases are additional, and unreported, examples of BMP use in the dog that I personally have experience with.

**Femoral fracture.** This dog had a re-fracture of an infected, torsional malunion that occurred 1-month after plate removal in a 1.5 year old MC German Short-Haired Pointer. Re-fracture occurred at the original fracture location due to less than ideal cortical remodeling that was present from the original repair. In this case re-plating of the fracture (and correction of the malunion) was accompanied by rhBMP-2 delivered locally in a synthetic apatitic calcium phosphate carrier (α-BSM™; Etex Corporation, Cambridge, MA). Healing with a robust amount of callus was evident by 6 weeks postoperatively, and by 1.3 years after surgery, the fracture to be solidly healed with ongoing recanalization of the medullary cavity.

**Elbow arthrodesis.** This 2 year old MC Pomeranian had a complication associated with bandaging of the forelimb post radial/ulnar fracture fixation where the entire olecranon was lost due to pressure necrosis. The dog could not stand on the limb due to absence of triceps muscle support. The elbow joint was successfully fused using an rhBMP2 - collagen sponge - TCP composite matrix, and stabilized with plate fixation. Fusion occurred rapidly, with robust callus observed by 11 weeks postoperatively.

**Distal radial atrophic nonunion.** This nonunion occurred after unsuccessful attempts at fracture fixation in a 2 year old MC Pomeranian (same dog as the arthrodesis, but opposite limb). After debridement of the nonunion site, the 1.5-mm gap was filled with an rhBMP2 - collagen sponge - TCP composite matrix, and stabilized with a transarticular circular external skeletal fixator (CESF). The gap filled rapidly, and bone remodeling was evident by 17 weeks postoperatively. At this stage, however, there was concern that there was insufficient bone present at the proximal extent of the graft/bone junction for unsupported weight bearing. The CESF was dynamized and additional rhBMP-2 was delivered percutaneously via injection; the BMP was delivered locally in a synthetic apatitic calcium phosphate carrier (α-BSM™; Etex Corporation, Cambridge, MA). By 7 months postoperatively the CESF was removed and robust bone remodeling was observed over the entire graft site.

**Acute mandibular reconstructions.** Two mandibular lesions (ossifying epulis and odontoma) have been treated via partial mandibulectomy and immediate mandibular reconstruction. In one case (ossifying epulis) in a 5 year, MC mixed breed dog, rhBMP-2 was delivered in a synthetic calcium phosphate carrier (α-BSM™; Etex Corporation, Cambridge, MA) in combination with stabilization across the gap with a miniplate. In the other case (odontoma), the mandibular gap was filled with rhBMP-2 - collagen sponge - TCP composite matrix, in combination with plate fixation. New bone was identified within the gap by 8 weeks postoperatively, and continued remodeling was present at recheck examination up to 1.5 years. One very important caveat needs to be presented, that of the principles of fracture fixation and nonunion management, which still cannot be overlooked. Use of the BMPs in less than ideal circumstances will not correct for a surgeon’s errors of fixation, which is an identical finding to usage of the more widely used autogenous cancellous grafting procedures.

As noted, the rhBMPs have only recently become approved for clinical use in both Europe and the USA (2001 and 2002), and only for limited specific indications (single level spinal fusion, acute tibial fracture us-
ing intramedullary nail fixation, and long bone nonunions). The major limiting factor for this product’s use in veterinary medicine is their high cost. For example, the market price for the 4.2-mg rhBMP-2 product (INFUSE® Bone Graft) is approximately US$3,500. Manufacturers have, however, occasionally provided the rhBMPs at minimal cost for compassionate veterinary care.

REFERENCES