Fortigen™-P: A Novel Osteoinductive Bone Graft for Dental Applications: Moving beyond the clot

Helen Newman, Ph.D.[1,2], Larry Shimp, Ph.D.[2], Lindsay Zager, M.S.[1], Rocco Mele, D.V.M.[3]
[1]Veterinary Transplant Services, Kent, WA; [2]Progenica Therapeutics, Covington, WA; [3]Eastpoint Pet Clinic, Tucson, AZ

The three elements needed for effective bone healing are a scaffold, a signal, and cells. Freeze-dried demineralized bone matrix and mineralized cancellous bone chips supply a scaffold in the form of its trabecular structure, and a signal (osteoinductivity) in the form of native growth factors. When placed in a site with vascular access, there are sufficient cells present for healing. A clot provides little in the way of scaffold, and thus adequate return of bone height cannot be achieved with clot alone. To further enhance bone healing, an effective method is to add additional growth factors to graft materials to increase osteoinductivity (OI). Synthetic bone grafts do not contain growth factors. Bone allograft is available that does contain osteoinductive growth factors (Periomix). A commercially available manufactured OI growth factor is also available, known as Infuse®. Infuse contains recombinant human Bone Morphogenic Protein-2 (rhBMP-2) in liquid form that is added to a collagen sponge carrier. The veterinary version is known as Truscient®. Although rhBMP-2 can cause a dramatic increase in bone formation, it is not bound to the carrier scaffold, and so is free to migrate away after implantation. This disadvantage has led to extraskeletal bone growth and other adverse effects including inflammation, swelling, and radiculopathy. Although natural bone graft contains many growth factor types, including BMP-2, it contains relatively low concentrations of the growth factors, so healing is not as robust as with Infuse/Truscient. This current study evaluates a novel approach to solving the problem of adding and retaining growth factor signals by augmenting a natural bone product. Periomix allograft is surface-coated with an effective concentration of osteoinductive signals that are anchored to the surface and thus will remain in the site. We refer to this enhanced allograft product as Fortigen™

We first examined Fortigen's effectiveness *in vitro*. Control (non-coated allograft) and BMP-2 were compared to investigational particles (Fortigen™-P coated allografts) for inductivity using an Alkaline Phosphatase Assay (ALP) (Han et al., 2003)[1]. This *in vitro* ALP method is a validated model for assessment of OI. It is based on the ability of inductive agents to transform mesenchymal stem cells into osteoblasts. In ALP cell cultures, Fortigen™-P had significantly higher OI when compared to the uncoated control particles. Furthermore, the OI of Fortigen™-P was found to be similar to the OI of BMP-2-containing positive control cultures (p-value=0.102 at the non-inferiority margin of 15%; n=3). The data show that these surface modifications can result in substantial increases in standard markers of OI *in vitro*. Thus, the product design has the potential benefit of inducing and potentially accelerating bone healing locally without the risk of signaling molecules leaving the site.

Based on the OI data and cell viability data in culture, we proceeded with compassionate use cases (with expected difficulties). Nine cases in need of sinus or ridge augmentations were selected to receive the Fortigen™-P bone graft materials. These cases were followed up until treatment outcomes had been determined. None of the cases had any device-related events.

All cases had accelerated and robust bone formation, some as early as two weeks. The quality of bone and soft tissue were judged to be excellent and the success rate was 100%. Average clinical and radiographic healing was seven weeks (range from 6-8 weeks).

Additionally, two cases of acute maxillary facial injuries were treated with Fortigen™-P. A case of premaxilla reconstruction and a case of mandibular fracture received Fortigen™-P. Despite the challenging conditions of both cases, successful healing signs were observed as early as 6 days post-op. The X-ray of the premaxilla reconstruction case at 5 weeks post-op demonstrated successful healing. In the mandibular fracture case, radiographic success was seen as early as day 20, and the later X-rays confirmed this success. In both traumatic fracture cases, no device-related events were reported.

We compared our data to historical data where rhBMP2 was used in similar cases (table). The data suggests that Fortigen™-P's effectiveness is not inferior to rhBMP2. Collectively, the *in vitro* and *in vivo* data to date provide compelling evidence that Fortigen™-P is exceedingly safe and is not inferior to BMP2. Additional studies are warranted to add to the data collected thus far; however these current safety and effectiveness features make it an excellent choice for bone grafting applications.

Indication/Procedure	FORTIGEN-P	rhBMP -2 (literature references)	FORTIGEN is: Not inferior to BMP-2	FORTIGEN is: Safe (no device-related events)	Number of cases
In Vitro ALP studies			Yes	NA	3
Mandibular fracture	12 weeks	12 weeks (2,3)	Yes	Yes	2
Dental augmentation	6-8 weeks	12 weeks (4, 5)	Yes*	Yes	9

1. Han B, Tang B, Nimni ME. Quantitative and sensitive in vitro assay for osteoinductive activity of demineralized bone matrix. J Orthop Res 2003;21(4):648-54.
2. Arzi B, Verstraete FJ, Huey DJ, Cissell DD, Athanasiou KA. Regenerating Mandibular Bone Using rhBMP-2: Part 1-Immediate Reconstruction of Segmental Mandibulectomies. Vet Surg 2015;44(4):403-9.
3. Verstraete FJ, Arzi B, Huey DJ, Cissell DD, Athanasiou KA. Regenerating Mandibular Bone Using rhBMP--2: Part 2-Treatment of Chronic, Defect Non-Union Fractures. Vet Surg 2015;44(4):410-6.
4. Cha JK, Lee JS, Kim MS, Choi SH, Cho KS, Jung UW. Sinus augmentation using BMP-2 in a bovine hydroxyapatite/collagen carrier in dogs. J Clin Periodontol 2014;41(1):86-93.
5. Jones AA, Buser D, Schenk R, Wozney J, Cochran DL. The effect of rhBMP-2 around endosseous implants with and without membranes in the canine model. J Periodontol 2006;77(7):1184-93.