Biomimetic Hematoma: Novel Carrier Delivers Extremely Low Dose rhBMP-2 for Highly Effective Healing of Large Bone Defects in Goats

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Purpose: The management of patients with large bone defects remains one of the most challenging clinical problems. One of the most promising treatments is the use of recombinant human bone morphogenetic protein 2 (rhBMP-2) delivered on an absorbable collagen sponge (ACS). However, it uses extremely high doses of BMPs, and has been associated with severe side effects, such as the inability of the collagen sponge to contain the rhBMP-2, allowing it to leach out into surrounding tissues. The fracture hematoma naturally serves as a scaffold that activates a cascade of biological events to initiate bone repair. Studies have shown that the removal of hematoma delays fracture healing, and that the structural properties of it, such as the porosity and thickness of fibrin fibers, influences bone repair. Our previous rat study demonstrated an ex vivo–created "biomimetic hematoma" (BH) that mimics the intrinsic structural properties of normal fracture hematoma, and consistently and efficiently enhanced the healing of large bone defects at extremely low doses of rhBMP-2 (0.33 μg). The aim of this study was to test if an extremely low dose of rhBMP-2 delivered within BH can efficiently heal large bone defects in goats.

Methods: Goat 2.5-cm tibial defects were stabilized with circular fixators, and divided into groups (n = 2-3): 2.1 mg rhBMP2 delivered on an ACS, 52.5 μg rhBMP-2 delivered within BH, and empty group. BH was created using autologous blood with a mixture of calcium and thrombin at specific concentrations. Healing was monitored with radiographs. After 8 weeks, femurs were assessed using micro-CT. Histology is in progress.

Results: Using 2.1 mg on ACS was sufficient to heal 2.5-cm bone defects. Empty defects resulted in a nonunion after 8 weeks. Radiographic evaluation showed earlier and more robust callus formation with 97.5% (52.5 μg) less of rhBMP-2 delivered within the BH, and all tibias were fully bridged at 3 weeks. The bone mineral density was significantly higher in defects treated with BH than with ACS. Defects in the BH group had smaller amounts of intramedullary and cortical trabeculation compared to the ACS group, indicating advanced remodeling.

Conclusion: Consistent with our study in rats, the results confirm that the ex vivo BH is able to mimic the function of innate fracture hematoma, which is the natural reservoir for rhBMP-2 and many other growth factors essential for bone healing, while also more efficiently regulating their release into the defect. The delivery of rhBMP-2 within the BH was much more efficient than on an ACS. Not only did the large bone defects heal consistently with a 40× lower dose of rhBMP-2, but the quality of the healing was also superior in the BH group based on the callus size and the bone morphometric parameters at 8 weeks. These findings should significantly influence how rhBMP-2 is delivered clinically to maximize the regenerative capacity of bone healing while minimizing the dose required. This would reduce the risk of adverse effects associated with BMPs, the treatment costs, and the nonunion rate.