RECOMBINANT HUMAN BONE MORPHOGENETIC PROTEIN-2 (rhBMP-2) INDUCES COUPLED ALLOGRAFT BONE REMODELING IN A FEMORAL SEGMENTAL DEFECT USING A CANINE MODEL

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Introduction: Frozen bone allografts are commonly used to reconstruct massive skeletal defects. Unlike autogenous bone grafts, allografts do not cause donor site morbidity and are readily available (1). The most common complications following allograft placement are delayed or non-union at either one or both allograft-host bone junctions, and allograft fractures (2). Bone morphogenetic proteins are signaling molecules that belong to the transforming growth factor β family, and have osteoinductive abilities (3). This study was designed to determine the effects of recombinant human bone morphogenetic protein-2 (rhBMP-2) compared to the “gold” standard, autogenous cancellous bone graft, on femoral allograft-host bone union and allograft remodeling in a canine model.

Material and Methods: Twenty-one mature dogs of similar size and weight were used. A 6-cm mid-diaphyseal section of the femur was removed and replaced with a frozen allograft of the same size stabilized with an interlocking nail in one randomly selected femur of each dog. The contralateral femur served as untreated (INTACT) control. All animals were randomly divided into three groups of seven animals. The first group received a 2.5 x 7.5 cm absorbable collagen sponge (ACS) loaded with 0.92 mg rhBMP-2 in buffer (BMP group). The second group was treated with a 2.5-cm³ autogenous cancellous bone graft as positive control (CBG group). The third group received an ACS loaded with buffer solution alone as negative control (ACS group). The allograft-host bone junctions and the mid-diaphyses of the allografts were wrapped with rhBMP-2/ACS, buffer/ACS, or ACS simply, in order to test the influence of rhBMP-2 on microstructure of new bone tissue formed on the allograft. The dogs received daily oral administration of tetracycline as a bone laid down marker. All dogs received daily oral administration of tetracycline until sacrifice at 24 weeks to label new bone formation. After harvesting both femurs, longitudinal sections of proximal and distal allograft-host bone junctions and transverse sections of allografts were ground to a thickness of 100 μm and evaluated using fluorescent light microscopy. Histomorphometric parameters measured were new bone formation, osteon radius (transverse section) or osteon width (longitudinal section), pore diameter of new bone, and porosity of original and new bone. All regions of interest were divided into endosteal, midcortical and periosteal areas. Data for all parameters were compared among and within groups using one-way analysis of variance followed by a post-hoc t-test when significant differences (p < 0.05) were found.

Results: Histomorphometric analyses of longitudinal sections revealed significantly more new bone formation and greater osteon width in the allograft-host bone junctions in the BMP group compared to the CBG group. Both groups had significantly higher values for these parameters than the ACS group. In the allograft, new bone formation and osteon radius/osteon width were similar for all three treatment groups, however in host bone, these parameters were significantly higher in the BMP group than in the CBG and ACS groups. New bone formation and osteon radius/osteon width were significantly higher in host bone, junctions and allografts in all three-treatment groups compared to the contralateral control (Fig. 1). Porosity in CBG and ACS groups was significantly higher compared to the BMP and INTACT group, which were similar (Fig. 2). The largest pore diameters were present in transverse sections of allografts in the CBG group. The smallest pore diameters of all groups occurred in allografts and host bone in the BMP group. In the three treatment groups, new bone formation was significantly higher in host bone and junctions. New bone formation in the allograft was similar for all three treatment groups.

Discussion: Similar new bone formation and osteon radius/osteon width in the allograft revealed similar osteoinductive activity in BMP, CBG and ACS groups, all with higher activity compared to the INTACT group. In the allograft-host bone junctions and host bone, the greatest osteoinductive influence with the highest new bone formation occurred in the BMP group which also showed better allograft host bone union than the other two groups. Radiographic analysis and mechanical testing previously reported confirmed the histomorphometric results (4). Radiographs and mechanical testing revealed that junctions in the BMP group were completely united and stronger compared to CBG and ACS groups. Higher porosity and larger pore diameters in the allografts of CBG and ACS groups suggested higher bone resorption activity in these groups compared to the BMP group. CBG and ACS groups revealed less balanced bone formation and bone resorption in the allografts. The histomorphometric analysis of the three groups evaluated in this study revealed that rhBMP-2 led to coupled remodeling of the allograft with balanced bone formation and resorption. Based on the results as shown, rhBMP-2 appears to be a better alternative to autogenous cancellous bone grafts for allograft incorporation in massive femoral segmental bone defects.

Figures 1 and 2. Mean of proximal and distal longitudinal sections. Values are mean ± SEM. Means with different upper case letters within a grouping are significantly different from each other.

Figure 1. Highest amount of new formed bone (p<0.05) was present in BMP group in host bone and junctions. New bone formation in the allograft was similar for the three treatment groups.

Figure 2. Porosity in all regions was significantly higher in CBG and ACS groups compared to BMP and INTACT groups, which showed similar values in host bone and allograft.

References:

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