COMPARISON OF HEALOS®/BONE MARROW TO INFUSE® (rhBMP-2/ACS) WITH A COLLAGEN-CERAMIC SPONGE BULKING AGENT AS GRAFT SUBSTITUTES FOR LUMBAR SPINE FUSION

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INTRODUCTION: Autogenous bone graft is considered the gold standard graft material for spine fusion. Complications with its use, however, may occur as many as 30% of patients. Additionally, the amount and quantity of autogenous bone graft is limited and may be insufficient, particularly in arthrodesis over multiple segments. Furthermore, the rate of nonunion using autogenous bone graft has been reported to range from 5% to 35%. To solve these problems, a variety of bone substitutes and tissue-engineering strategies are already being used and others are still under development. Unfortunately, there are few direct comparison experiments between various substitutes in the same model which could help establish the relative efficacy between various graft substitutes.

Recombinant bone morphogenetic protein–2 (rhBMP-2) delivered on a collagen sponge (INFUSE®, Medtronic Sofamor Danek), has been recently approved by the FDA for use inside an anterior lumbar interbody fusion cage and preclinical studies have demonstrated its efficacy with the addition of bulking agents in posterolateral spine fusion. Concurrently, there have been animal and some human studies suggesting that autogenous bone marrow delivered on a collagen-hydroxyapatite sponge (Healos®, Depuy, Raynham, MA) has been successful in posterolateral lumbar spine fusions. These studies with Healos were not part of an FDA study and did not use CT scans to evaluate fusion as in the BMP-2 studies. In addition, many have questioned the osteogenicity of bone marrow on any scaffold to effectively replace autogenous bone graft for posterolateral spine fusion which is one of the most challenging bone healing environments.

The purpose of this experiment was to use a validated animal model of posterolateral spine fusion to directly compare the efficacy of two bone graft substitutes. We compared bone marrow delivered on the Healos collagen-hydroxyapatite scaffold with that of rhBMP-2 delivered on a collagen sponge wrapped around a compression resistant collagen-ceramic sponge.

METHODS: Adult NZW rabbits (n=24) underwent posterolateral spine arthrodesis at L5-L6 under general anesthesia. A Wiltes paraspinal muscle-splitting approach was used and the transverse processes were decorticated with an electric burr. Healing Group: 12 rabbits received Healos collagen-hydroxyapatite matrix (10x30x5 mm, two per side) with 3.0mL of bone marrow.(ratio 1:1) Bone marrow was aspirated from the posterior iliac crest and 200 units of heparin were added. One mL of bone marrow was used to count the number of nucleated cells. BMP-2 INFUSE Group: 12 rabbits received rhBMP-2 (1.5mL 0.43mg/mL per side) delivered on an absorbable collagen sponge (ACS) wrapped around a compression resistant collagen-ceramic sponge (15% HA/85% TCP, 10x30x5 mm, one per side). No autogenous iliac crest bone graft was harvested in either group.

The rabbits were euthanized after 12 weeks; the spines were evaluated by manual palpation, plain radiographs, CT scan, and tensile mechanical testing. Relative strength and stiffness (± SEM) were calculated as the ratio of the value at the operative level compared to that at the adjacent unfused segment in each rabbit. A Fisher exact test was used to compare the frequency of nonunions in each group. A two-tailed t-test was used to measure the significance of difference in mechanical properties between groups.

RESULTS: The bone marrow had a mean total nucleated cell count of 9±107 cells. All rabbits (12/12) in the BMP-2 Group achieved solid spinal fusions by manual palpation and radiographs. In contrast, all spinal fusions (0/12) were achieved by manual palpation or radiographs in any of the rabbits in the Healos Group. The CT scans of rabbits from the Healos group showed some small bone near the transverse processes but none of them formed a continuous fusion mass (left side photo). In contrast, CT scans of all spines from the rabbits in the BMP-2 Group showed complete graft incorporation with continuous bone connecting the transverse processes bilaterally (right side photo). The biomechanical testing results correlated with the manual palpation and radiographic evaluations. The relative strength of the fusion segment was greater in the BMP-2 Group compared to the Healos Group, 3.86 ± 0.48 vs. 1.55 ± 0.21 (p=0.0003). The 95% CI for the difference in relative strength of the BMP-2 Group was 1.21-3.42 times more than the Healos Group. The relative stiffness of the fusion segment was greater in the BMP-2 Group compared to the Healos Group, 2.32 ± 0.20 vs. 1.24 ± 0.11 (p=0.0002).

DISCUSSION: The results of this study showed that INFUSE (rhBMP-2/ACS) consistently produced spine fusion (72%) when wrapped around a compression resistant collagen-ceramic sponge consistent with multiple previous reports with rhBMP-2 in a variety of spine fusion models with other carriers.(1) The Healos collagen-hydroxyapatite matrix augmented with autogenous bone marrow produced only trace amounts of bone and did not achieve a complete spine fusion in any rabbit. The literature is conflicting with regards to the efficacy of autogenous bone marrow with ceramic carriers for spine fusion.(2,3) Muschler et al reported failure to achieve fusion when collagen-ceramic with bone marrow was implanted in a canine model of lumbar spine fusion.(3) Tay et al showed 100% spine fusion was produced by the Healos collagen-hydroxyapatite scaffold augmented with bone marrow in the same rabbit model used in our study.(2,4) The Tai study reported the number of nucleated cells from bone marrow aspirations taken from all the long bones of the rabbit, but did not report the ratio of bone marrow volume to size of carrier. Our present study used slightly less nucleated cells, possibly since a more clinically relevant bone marrow aspiration technique from the iliac crests was used. This could in part explain the different result with the Tai study, although we feel this is unlikely to explain such a drastically different result. Alternatively, fusion assessment in the Tai study was done primarily by plain radiographs which are not reliable for assessing spine fusion. The over-reliance on plain radiographs rather than CT scans in the Tai study might explain why their biomechanical testing did not differentiate fibrous unions from bone fusions in that study.

Posterolateral spine fusion has proven to be one of the most challenging bone healing environments in animals and humans. Previous studies have demonstrated that purely osteoconductive scaffolds such as coral and ceramic composites, while acceptable for long bone fractures and defects, have not been successful as stand-alone substitutes for posterolateral spine fusion. Even the addition of bone marrow has not appeared to sufficiently enhance a purely osteoconductive matrix to achieve consistent posterolateral spine fusion. In contrast, the addition of a potent osteoinductive protein, such as rhBMP-2, was able to consistently produce spine fusion in this model.

In conclusion, this study raises doubts about the ability of bone marrow and an osteoconductive scaffold such as Healos to provide an effective substitute for autogenous bone graft in a validated model of posterolateral spine fusion. This study should also raise caution about reports that suggest that bone marrow can provide a similar level of osteogenic potential to osteoinductive proteins such as BMP-2. Further studies are warranted with appropriate assessment of bone fusion in higher animal models.

REFERENCES:

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