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A porcine collagen-derived matrix as a carrier for recombinant human bone morphogenetic protein-2 enhances spinal fusion in rats

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Abstract

BACKGROUND CONTEXT: Recombinant bone morphogenetic proteins (rhBMPs) have been used successfully in clinical trials. However, large doses of rhBMPs were required to induce adequate bone repair. Collagen sponges (CSs) have failed to allow a more sustained release of rhBMPs. Ongoing research aims to design carriers that allow a more controlled and sustained release of the protein. E-Matrix is a injectable scaffold matrix that may enhance rhBMP activity and stimulate bone regeneration.
PURPOSE: The purpose of this study was to test E-Matrix as a carrier for rhBMPs in a CS and examine its feasibility in clinical applications by using a rat spinal fusion model.
PATIENT SAMPLE: A total of 80 Lewis rats aged 8–16 weeks were divided into nine groups.
STUDY DESIGN/SETTING: Rat spinal fusion model.
OUTCOME MEASURES: Radiographs were obtained at 4, 6, and 8 weeks. The rats were sacrificed and their spines were explanted and assessed by manual palpation, high-resolution micro-computed tomography (micro-CT), and histologic analysis.
METHODS: Group I animals were implanted with CS alone (negative control); Group II animals with CS containing 10 μg rhBMP-2 (positive control); Group III animals with CS containing 3 μg rhBMP-2; Group IV animals with CS containing 3 μg rhBMP-2 and E-Matrix; Group V animals with CS containing 1 μg rhBMP-2; Group VI animals with CS containing 1 μg rhBMP-2 and E-Matrix; Group VII animals with CS containing 0.5 μg rhBMP-2; Group VIII animals with CS containing 0.5 μg rhBMP-2 and E-Matrix; and Group IX animals with CS and E-Matrix without rhBMP-2.
RESULTS: Radiographic evaluation, micro-CT, and manual palpation revealed spinal fusion in all rats in the BMP-2 and E-Matrix groups (IV, VI, and VIII) and high-dose BMP-2 groups (II and III). Four spines in the 3 μg rhBMP-2 group (V) fused, and one spine in the 0.5 μg rhBMP-2 group (VII) exhibited fusion. No spines were fused in Groups I (CS alone) and IX (E-Matrix alone). The volume of new bone in the area between the tip of the L4 transverse process and the base of the L5 transverse process in Group IV was equivalent to the volumes observed in Group II.
CONCLUSION: E-matrix enhances spinal fusion as a carrier for rhBMP-2 in a rat spinal fusion model. The results of this study suggest that E-Matrix as a growth factor carrier may be applicable to spinal fusion and may improve rhBMP-2's activity at the fusion site.

Keywords: E-matrix; Carrier; Bone morphogenetic protein; Spinal fusion; Rat model

FDA device/drug status: approved for this indication (E-Matrix).

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Introduction

Studies on animal models and clinical trials have demonstrated the osteoinductive effects of recombinant bone morphogenetic proteins (rhBMPs) in various surgical procedures, such as fracture repair, healing of critical-size bone defects, and spinal fusion [1–9]. However, the results of clinical trials show that high doses of BMPs are required to induce adequate spinal fusion because the molecules are soluble and can diffuse away from the fusion site easily and become inactivated in vivo [10]. BMPs are highly expensive and their usefulness is therefore limited; moreover, they may cause local adverse effects such as unwanted ectopic bone formation and inflammation, particularly when used in the cervical spine [11,12].

A number of strategies are being developed to provide a safer, less expensive, and more efficacious spinal fusion using rhBMP. Some ongoing strategies aim at designing carriers that allow a more controlled and sustained release of the protein so that the growth factor concentration is maintained locally within the therapeutic range.

A collagen sponge (CS) has been used as a carrier matrix for rhBMPs over the last several years because of its excellent biocompatibility, ability to degrade into physiological end-products, and suitable interaction with cells and molecules. Both basic and clinical studies have demonstrated its safety [13–15]. Although collagen sponges allow a longer local retention of rhBMPs at the implantation site than a buffer alone [2], there are perhaps more optimal carriers that may induce the maximum therapeutic effect.

E-Matrix is an injectable scaffolding matrix for cellular attachment derived from porcine skin collagen. It has been developed to accelerate wound healing in diabetic foot ulcers [16]. Prior studies on E-Matrix have shown that it enhances the production of growth factors, such as transforming growth factor-β-3 and vascular endothelial-derived growth factor receptors [17]. It is assumed that the interaction of host cells with E-Matrix leads to altered cellular responses, accelerating tissue regeneration. Prior clinical trials have shown E-Matrix to be safe [16]. We hypothesize that the incorporation of E-Matrix and rhBMP-loaded absorbable collagen sponge is feasible, that it allows a more sustained release of rhBMPs than the collagen sponge alone, and that the combination will stimulate more efficacious bone regeneration.

The purpose of this study was to develop E-Matrix with a collagen sponge as a carrier matrix for rhBMPs and examine its feasibility in clinical application by using a rat spinal fusion model.

Materials and methods

E-Matrix is a biocompatible scaffold for cellular attachment; it is composed of gelatin alpha chains derived from porcine skin collagen stabilized by copolymerization with a high-molecular weight polysaccharide (500 kDa dextran). It is designed such that the open polar alpha chains have the maximum possible number of hydrogen bonding sites for polar amino acids. This open polar structure was designed to mimic the open structure of early embryonic dermis [16] (Fig. 1). Pioneer Surgical Orthobiologics (Greenville, NC) provided the E-Matrix for this study.

Rat spinal fusion model

Preparation of carrier matrices

RhBMP-2 was applied to a CS carrier (Helistat; Integra Life Sciences, Plainsboro, NJ) with or without E-Matrix

EVIDENCE & METHODS

Context

Recombinant human bone morphogenetic protein (rhBMP) for spinal fusion has demonstrated efficacy in human trials when used in the anterior lumbar spine. The currently available forms use a collagen sponge carrier. The optimum use of rhBMP (concentration, carrier, application timing, etc) in different fusion techniques remains unclear. Negative side effects of rhBMP, such as graft resorption, sterile fluid collections, and airway swelling in the cervical spine, are suspected to be dose and application dependant.

Contribution

The current study evaluated the efficacy of an additive carrier, called E-Matrix, to rhBMP-2 in a rat spinal fusion model. The investigators hypothesized that previously suggested efficacy of E-Matrix as a growth factor enhancer might augment the effects for rhBMP-2. The authors compared nine different combinations of combinations of rhBMP-2 with E-matrix. They detected improved radiographic fusion scores and the fusion rates with some combination preparations at lower than usual concentrations of rhBMP.

Implications

The direct clinical implications for human use of this animal study are necessarily limited. Nor is this study comparable to most animal spine-BMP research which has been performed using a rabbit model. Also, the long-term safety of the dosages and combinations used have not been assessed in animal or human applications. However, assuming further research can adequately address these limitations, E-matrix or a similar additive carrier may augment fusion at a lower, and perhaps safer, concentration of rhBMP-2.

—TSJ Editors