Evaluation of spinal fusion capacity by a biodegradable nanogel

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ABSTRACT: Background: Although surgical technique and instrumentation within the field of spine surgery have improved in recent years, pseudarthrosis still occurs in 10-15% of patients undergoing spine fusion. Furthermore, the morbidity and postoperative pain of approximately 500.00 autogenous bone grafting procedures performed annually has prompted the development of bone graft substitutes as alternative treatment approaches. Recombinant human BMP-2 (rhBMP-2) has been shown to facilitate successful healing in long bone defects and spinal arthrodesis models. However, efficient healing requires supraphysiologic doses, which may lead to surgical complications. This study investigated the capability of a biodegradable nanogel containing a BMP-2-binding epitope to elicit spine fusion in a rat posterolateral arthrodesis model. Methods: One hundred twelve female Sprague-Dawley rats underwent a posterolateral intertransverse lumbar spine fusion treated with one of the following scaffolds: non-BMP-2-binding nanogel (E3PA), BMP-2-binding nanogel (BMP-2PA) or absorbable collagen sponge (ACS). Scaffolds were preloaded with either 0, 0.1, or 1.0 μg rhBMP-2 (per animal). Bone growth/fusion was assessed using plain radiographs and quantitated via manual palpation. Results: When preloaded with 0.1 μg or 1.0 μg rhBMP-2, the BMP-2PA elicited significantly higher fusion scores than ACS equivalently preloaded with rhBMP-2. The BMP-2PA preloaded with 1 μg rhBMP-2 elicited a fusion rate of 100%, with an average fusion score similar to that elicited by 10 μg rhBMP-2 on ACS (positive control). In comparison, 1 μg rhBMP-2 loaded on to ACS and E3PA resulted in fusion rates of 65% and 75%, respectively. Clinical Relevance: The use of this nanogel allows for a 10-fold reduction in the concentration of rhBMP-2 required for a 100% fusion rate in our model.

Background
1. The use of autogenous iliac crest bone graft has historically been the gold standard to achieve fusion. However, 60% of patients continue to complain of hip pain 2 years after surgery.1
2. Recombinant Bone Morphogenetic Protein-2 (rhBMP-2) has been used as an alternative to iliac crest bone graft. However, several complications have been reported: • Cervical spine: graft subsidence, seam formation • Lumbar spine: bone resorption, graft migration
3. Absorbable collagen sponge (ACS) is the FDA-approved carrier for rhBMP-2 and has widely been used in lumbar spine fusion surgery. • Optimizing delivery of the rhBMP-2 may reduce the dosage required for successful spine fusion.
4. Nanofiber scaffolds have been shown to increase osteoblast function and decrease fibroblast adhesion. • In this study, a biodegradable nanogel composed of peptide amphiphiles was developed that has the capacity to bind BMP-2 (BMP-2PA) 1,2, • E3PA = non-BMP-2-binding control nanogel • In vivo, nanofibers from both gels are gradually degraded by surrounding cells, leaving the bony fusion mass.

Methods
• 112 female Sprague-Dawley rats underwent posterolateral intertransverse lumbar spine fusion, graft materials were implanted bilaterally over deocated L4-L5 transverse processes. • Graft materials included E3PA (non-binding nanogel), BMP-2PA (BMP-2-binding nanogel), ACS (absorbable collagen sponge). Each group was further divided into subgroups with scaffolds preloaded with 0, 0.1, or 1.0 μg rhBMP-2 per animal. Ten μg rhBMP-2/ACS served as a positive control. • Fusion was assessed 8 weeks post-surgery using plain AP radiographs and manual palpation. • Spines were scored by three blinded observers using a previously established scoring system. B1: unbridged, B2: unilateral bridging, B3: bilateral bridging with abundant bone. Spines which scored an average of ≥1.0 were considered successfully fused.

Results
• 1.5 fold reduction in the concentration of rhBMP-2 required for a 100% fusion rate in our model.

Summary and Conclusions
• E3PA performs superior to ACS when preloaded with equivalent [rhBMP-2]. • BMP-2PA performs superior to E3PA when preloaded with equivalent [rhBMP-2]. • The presence of the BMP-2-binding epitope provides a biological advantage for bone formation/fusion. • The BMP-2PA with no exogenous rhBMP-2 was sufficient to elicit spine fusion in some but not all animals. • The BMP-2PA preloaded with 1 μg rhBMP-2 performed as well as ACS preloaded with 10 μg rhBMP-2. Therefore, the use of this nanogel allowed for a 10-fold reduction in the concentration of rhBMP-2 required for a 100% fusion rate in our model.

References

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