

POSTEROLATERAL INTERTRANSVERSE LUMBAR FUSION IN NONHUMAN PRIMATES USING OP-1 PUTTY: EFFECT OF DOSE CONCENTRATION ON FUSION RATE

Louis Jenis, MD ¹, Bryan Cunningham, MSc², Dean Falb, PhD³, David Hile, PhD³, Allen Pierce, BS³, Denis Schrier, PhD³, Elizabeth Goad, DVM, PhD³

¹The Boston Spine Group, Newton, MA, USA

²St. Joseph's Medical Center, Towson, MD, USA

³Stryker Biotech, Hopkinton, MA, USA



Biotech

INTRODUCTION:

- Posterolateral lumbar spinal fusion is a common clinical procedure.
- Bone morphogenetic protein-7 (BMP-7/OP-1) has shown promise as an alternative to autograft when administered as OP-1 Putty [1].
- While treatment with OP-1 appears effective [1], some question remains as to the optimal protein concentration.
- BMP concentration has significant implications for both safety and efficacy.
- A better understanding of effective dosing in a baboon nonhuman primate (NHP) could help optimize concentration in humans.
- The baboon NHP model provides the closest approximation to humans, while permitting collection of additional endpoints such as histology and biomechanics.

METHODS:

Animals and Experimental Groups

- Adult male baboons (n = 24), weighing an average of 26 ± 4.7kg were surgically prepared for instrumented (bilateral pedicle screw-rod fixation) PLF at the L4/L5 level and were evenly divided into six groups:
- Group 1: Autograft.** Iliac crest autograft was harvested and placed (4.5 cc/side – maximum feasible amount) across transverse processes
- Group 2: Carrier only.** Animals received carrier only consisting of type I collagen and carboxymethylcellulose (6 cc/side).
- Group 3: 0.33 mg/mL BMP-7.** Animals received carrier (6 cc/side) plus BMP-7 at 0.33 mg/mL concentration.
- Group 4: 1.0 mg/mL BMP-7.** Animals received carrier (6 cc/side) plus BMP-7 at 1.0 mg/mL concentration.
- Group 5: 2.0 mg/mL BMP-7.** Animals received carrier (6 cc/side) plus BMP-7 at 2.0 mg/mL concentration.
- Group 6: 4.0 mg/mL BMP-7.** Animals received carrier (6 cc/side) plus BMP-7 at 4.0 mg/mL concentration.
- BMP-7 concentration was determined using the following formula:

$$\text{BMP-7 Concentration (mg/cc)} = \frac{\text{BMP-7 Content (mg)}}{\frac{\text{OP-1 Putty Mass (g)}}{\text{OP-1 Putty Density (g/cc)}}$$

- Sacrifice euthanasia at 6 months, but animals were euthanized early (4 months) due to robust early bone formation in most groups

Outcome Measurements

- Radiographs:** Plain radiographs taken preoperatively, immediately postoperatively, and at 2, 3 and 4 months postoperatively
- Computed Tomography (CT):** Fine cut CT images obtained at 3 & 4 months postoperatively
- Biomechanical Testing:** Nondestructive biomechanical testing conducted including flexion and extension, lateral bending torsion
- Histology & Histomorphometry:** Histological and histomorphometric evaluations completed included Hematoxylin and Eosin (H&E), Macrophage Staining Method (HAM-56) and Villanueva Osteochrome Bone Stain
- Statistics:** Appropriate statistical analyses were carried out for each outcome measurement including Chi Square analysis for X-rays, and One-Way Analysis of Variance (ANOVA) with probability of least significant differences (PLSD) for biomechanical and histomorphometric data. Statistical results at p<0.05 are considered significant.

Figure 1: Fusion by CT

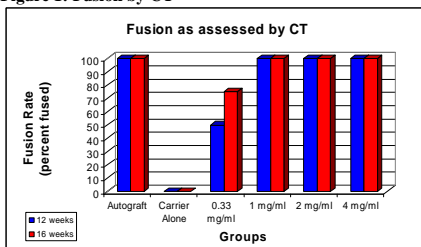


Figure 2: Sample CT Images (3 Month)

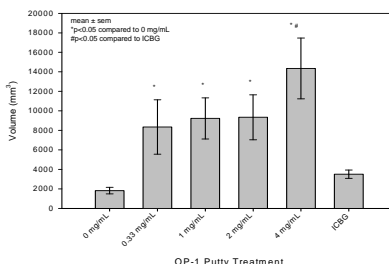
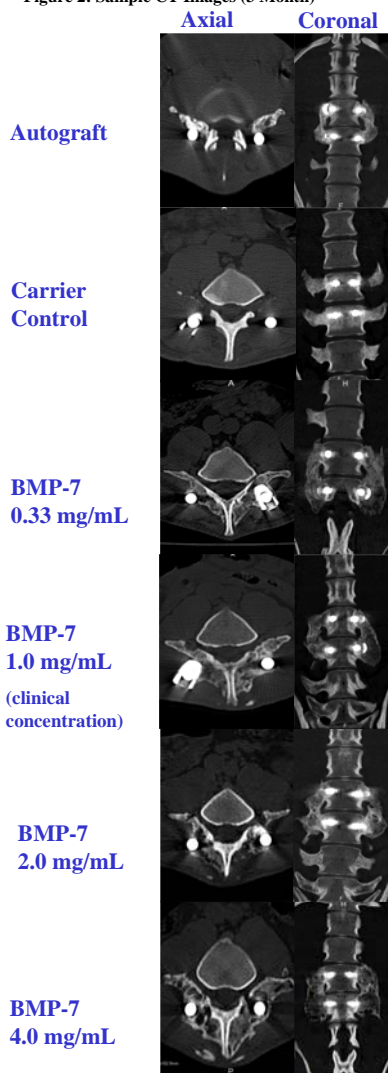


Figure 3: Total Fusion Volume by CT (4 months)

RESULTS:

- The surgical procedure was well tolerated by all animals
- There were no adverse events, neurologic, vascular or infection complications observed in any animal.
- Autograft animals demonstrated 100% fusion by 4 months, so animals were sacrificed early.
- Concentration dependent response observed:
 - No animals in carrier only group achieved fusion at any time point
 - 100% of animals in autograft group fused by 3 months
 - 100% of animals in the 1.0, 2.0 and 4.0 mg/mL BMP-7 groups fused by 3 months
 - 75% of the animals in the 0.33 mg/mL BMP-7 group fused by 4 months
- No significant differences in fusion observed comparing autograft and any of the BMP-7 groups except 0.33 mg/mL
- Using CT reconstruction, significant increases in bone volume were observed in the 1.0, 2.0 and 4.0 mg/mL BMP-7 groups
- Biomechanically, a significant reduction in range of motion during lateral bending was observed in all treatments groups compared with control group (carrier only)
- Some variability in histologic bone maturity was observed within and between treatment groups

DISCUSSION & CONCLUSION:

- BMP concentration is an important parameter in determining fusion rate
 - same graft volume with different BMP-7 concentrations yielded different fusion rates
- 0.33 mg/mL induced fusion in most animals at 4 months, and we expect would induce 100% fusion by 6 months
- 1.0 mg/mL (current clinical concentration) appears to be on the plateau of the concentration curve for BMP-7 in this model
 - Equivalent to autograft in most parameters
- Fusions observed on X-ray and CT were functional as indicated by the increased biomechanical rigidity
- Additional bone formation was observed at BMP-7 concentrations above 1.0 mg/mL, but no significant differences in primary outcomes measurements were observed
- Outcome measurements can provide different information:
 - Axial CT appears to show medial fusion not easily observed on plain X-ray
 - Histology shows much of autograft fusion mass seen on CT is unincorporated graft material
- Future work needs to address:
 - Effect of carrier volume
 - Effect of carrier material
 - BMP-7 release rate
 - Bone formation rate via CT
 - Fusion observed earlier than expected

References:

- Vaccaro, A. R., P. G. Whang, et al. (2007). "The safety and efficacy of OP-1 (rhBMP-7) as a replacement for iliac crest autograft for posterolateral lumbar arthrodesis: minimum 4-year follow-up of a pilot study." *Spine J.*

Disclosure information

Financial Disclosure
One or more authors is a current employee of Stryker Biotech and the study was sponsored by Stryker Biotech.

Regulatory Disclosure

The pharmaceuticals and/or medical devices for the use described in this presentation are currently not approved for use in this indication.