Biomechanical Evaluation of an Injectable and Biodegradable Copolymer P(PF-co-CL) in a Cadaveric Vertebral Body Defect Model

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A novel biodegradable copolymer, poly(propylene fumarate-co-caprolactone) [P(PF-co-CL)], has been developed in our laboratory as an injectable scaffold for bone defect repair. In the current study, we evaluated the ability of P(PF-co-CL) to reconstitute the load-bearing capacity of vertebral bodies with lytic lesions. Forty vertebral bodies from four fresh-frozen cadaveric thoracolumbar spines were used for this study. They were randomly divided into four groups: intact vertebral body (intact control), simulated defect without treatment (negative control), defect treated with P(PF-co-CL) (copolymer group), and defect treated with poly(methyl methacrylate) (PMMA group). Simulated metastatic lytic defects were made by removing a central core of the trabecular bone in each vertebral body with an approximate volume of 25% through an access hole in the side of the vertebrae. Defects were then filled by injecting either P(PF-co-CL) or PMMA *in situ* crosslinkable formulations. After the spines were imaged with quantitative computerized tomography, single vertebral body segments were harvested for mechanical testing. Specimens were compressed until failure or to 25% reduction in body height and ultimate strength and elastic modulus of each specimen were then calculated from the force–displacement data. The average failure strength of the copolymer group was 1.83 times stronger than the untreated negative group and it closely matched the intact vertebral bodies (intact control). The PMMA-treated vertebrae, however, had a failure strength 1.64 times larger compared with the intact control. The elastic modulus followed the same trend. This modulus mismatch between PMMA-treated vertebrae and the host vertebrae could potentially induce a fracture cascade and degenerative changes in adjacent intervertebral discs. In contrast, P(PF-co-CL) restored the mechanical properties of the treated segments similar to the normal, intact, vertebrae. Therefore, P(PF-co-CL) may be a suitable alternative to PMMA for vertebroplasty treatment of vertebral bodies with lytic defects.

Introduction

AT LEAST ONE MILLION new cases of cancer are diagnosed each year in the United States¹ and up to one-third of cancer patients develop spinal metastasis.² Vertebrae affected with lytic metastases are structurally weakened and are a source of severe pain.^{3,4} Furthermore, vertebrae with lytic metastases are at an elevated risk of burst fracture, which may lead to neurological compromise from the retropulsion of tumor or bone into the spinal canal. Prophylactic intervention to stabilize weakened vertebrae before a

pathological fracture is recognized as an important consideration in maintaining the quality of life in this patient population.⁵

Percutaneous vertebroplasty (PVP), advocated first for the treatment of metastatic lesions in 1987,⁶ is a minimally invasive, imaging-guided interventional technique, in which poly(methyl methacrylate) (PMMA) bone cement is injected into structurally weakened vertebrae to provide pain relief and mechanical stabilization. Over the past 20 years, the indications have been expanded and the technique has been applied for the treatment of an increasing population

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of metastatic patients.^{5,7} Clinically, PMMA has been the material of choice, however, there are several disadvantages associated with its use.^{8–13} PMMA has a relatively short injection time, in which the material can flow in a cohesive manner and stops flowing when it has become too viscous to be injected. In addition, the maximum curing temperature can exceed 100°C posing a risk of tissue injury. This risk is most concerning for the spinal cord and nerve roots, but may also affect vascular and peripheral nervous tissues that exist near the vertebrae. Additionally, PMMA has a higher modulus than trabecular bone, which can lead to stress shielding and resorption of bone or disc degeneration adjacent to the reconstruction. This can be especially problematic for osteoporotic spine patients since the vertebrae above and below the PMMA-treated vertebra may develop an increased risk of fracture.^{14–16} Since PMMA is a nondegradable material, it offers only nonbiological reconstruction. Therefore, it is not an appropriate choice for those vertebrae in which the treatment decision is to perform a biologic reconstruction and expect bone healing to occur.

To specifically address the concerns of high curing temperature and modulus mismatch, our group has synthesized a novel injectable and biodegradable copolymer, poly(propylene fumarate-co-caprolactone) [P(PF-co-CL)], which cures at near physiological temperature and has a compressive modulus on the same order of magnitude as trabecular bone.^{17,18} The copolymer formulation with 50/50 ratio of poly(propylene fumarate) (PPF) and poly(caprolactone) (PCL) was used based on previous studies demonstrating good biocompatibility and suitable mechanical properties for use as a synthetic bone substitute.^{18,19} The degradation rate of P(PF-co-CL) can be varied by changing the copolymer composition, molecular weight, and crosslinking parameters.^{20,21} The ability to tailor the degradation profile such that the materials can maintain their mechanical properties and mass over a time spectrum that ranges from several weeks to more than a year permits material selection that is appropriate for either a biological or nonbiological reconstruction, depending on the particular patient's clinical situation.

The current study was designed to compare P(PF-co-CL) to conventional PMMA bone cement in a clinically relevant simulated vertebral lytic defect cadaver model. The mechanical properties of vertebral bodies treated with different materials were analyzed to determine whether the novel injectable copolymer P(PF-co-CL) is a promising alternative filling material for metastatic vertebrae.

Materials and Methods

Four fresh-frozen cadaveric spine cadavers (age range 48–74 years; median age 55.3 years) were obtained from the anatomy department of Mayo Clinic. Spines were wrapped in saline-soaked gauze, sealed in plastic bags, and stored at –20°C until further use. Forty vertebral bodies from the cadaveric thoracolumbar spines (T2–L5) were randomly divided into four groups: intact vertebral body (intact control, $n=8$), simulated defect without treatment (negative control, $n=5$), defect treated with P(PF-co-CL) (copolymer group, $n=16$), and defect treated with poly(methyl methacrylate) (PMMA group, $n=11$).

Simulated metastatic lytic defect model

Except for the specimens in the intact group, the lateral side on each vertebral body was located and a small hole of ~3 mm in diameter was drilled to allow for the probe of the vertebroplasty instrument (Kyphon, Inc.) to be inserted (Fig. 1). An ~25% of the vertebral trabecular body's volume was removed from the center core using a small bone spoon through the lateral access hole. To obtain an accurate defect volume, the balloon from the vertebroplasty instrument was inserted into the center of the vertebral body through the lateral access hole and, using a predetermined volume calculated for each vertebral specimen based on measured geometries, was gradually inflated to reach the 25% desired defect volume. No endplate disruptions were observed in all specimens by visual visualization.

Defect filling

The intact and negative control specimens were left untouched throughout this process. The PMMA group was injected with a high-viscosity PMMA bone cement (DePuy Spine) using a syringe. Similarly, the copolymer group was injected with an *in situ* polymerizable formulation consisting of P(PF-co-CL) with 50/50 ratio of PPF to PCL. P(PF-co-CL) was synthesized using previously described methods.¹⁸ To crosslink the formulation, 54 mg of the initiator benzoyl peroxide was dissolved in 870 μ L of methyl methacrylate. The solution was mixed with 1.75 g of P(PF-co-CL) until the latter was completely dissolved. Then, 20 μ L of N,N-dimethyl-p-toluidine was added into the formulation to accelerate the reaction. After filling of the defects with material injection, the cadaveric spines were wrapped in saline-soaked gauze, sealed in a plastic bag, and stored at 4°C for a minimum of 24 h to allow further cement polymerization, while preventing significant cadaver specimen degradation.

Quantitative computed tomography scanning and imaging analysis

Following defect filling, the four cadaveric spines were scanned using a Siemens Somatom Definition scanner (Siemens). The spines were placed on top of a calibration phantom (Midways, Inc.) containing five rods of reference materials. DICOM images obtained during the scanning process were imported into the image analysis software Analyze™ (Biomedical Imaging Resource). The actual defect volume was measured and the volumetric bone mineral density (vBMD) of each vertebral body, excluding the defect, was calculated by converting gray-scale values (Hounsfield units) to equivalent K_2PO_4 density (ρ_{ash} , mg/cm³) from the calibration phantom.

Biomechanical testing

Individual vertebrae were dissected from the cadaveric spines and stripped of soft tissue using a scalpel. Posterior elements and intervertebral discs were also removed. The top and bottom regions of each vertebra were embedded with PMMA as previously described^{22,23} to ensure uniform loading during compression testing. Vertebral bodies were compressed using a material testing system (MTS 858 MiniBionix) at a rate of 5 mm/min.^{24–26} Preconditioning

FIG. 1. Procedure for bone defect model: Bone defects were performed through a lateral approach (A, B) in the vertebral bodies using a vertebroplasty balloon to reach a target defect volume of $\sim 25\%$ of the vertebral body (C). Color images available online at www.liebertpub.com/tea

of the specimens consisted of 10 cycles of compressive loading and unloading from 100 to 250 N to avoid any micromotion between the vertebrae-PMMA-MTS interface. Following preconditioning, the specimens were compressed to failure or up to a 25% reduction in vertebral height.

Force-displacement data were recorded at a rate of 102.4 Hz and stress-strain curves obtained. Figure 2 shows the compression experimental setup.

Ultimate strength was calculated as the first peak on the stress-strain curve and elastic modulus was calculated in the

FIG. 2. Mechanical testing setup used to create a compression fracture (25% reduction of intact vertebral height or until failure). (A) MTS setup and (B) enlarged illustration of the potted vertebral body-MTS configuration. MTS, material testing system. Color images available online at www.liebertpub.com/tea

linear region of the curve between 20% and 80% of the ultimate failure load.

Statistical analysis

All data are presented as means $\pm$ standard deviations (SDs). Statistical analysis was carried out using the SPSS 18.0 software package for windows (SPSS, Inc.). Analysis of variance and the Kruskal–Wallis *post hoc* test were used to test for significant differences in ultimate strength, elastic modulus, and defect volumes. A difference of $p < 0.05$ was considered statistically significant.

Results

Simulated lytic defects were successfully created in cadaveric vertebral bodies (Fig. 3A, B) and filled with either PMMA (Fig. 3C, D) or P(PF-co-CL) (Fig. 3E, F). A cross-sectional view of a gross examination (Fig. 3C) shows a densely packed PMMA material, as well as a completely intact interface with the surrounding trabecular bone. The corresponding quantitative computed tomography (QCT) image (Fig. 3D) shows boundaries between cancellous bone and the filling material. For defects filled with P(PF-co-CL), the material is seen to have permeated into the trabecular space around the defects creating a tight mechanical interlocking between the filling material and the surrounding bone.

The actual defect volume from the QCT scans was quantified to be $23.3\% \pm 6.2\%$ v/v, close to the initial desired volume of 25%. The percentage of bone defect volume showed no significant difference between the groups ($p > 0.05$). The vBMD of each vertebral body was also calculated from the K_2PO_4 density calibration phantom. Average vBMD (mg/cm^3) for the negative, intact, copolymer, and PMMA groups were 189 ± 27 , 173 ± 35 , 195 ± 24 , and 205 ± 24 , respectively.

The typical load–displacement representation for each group was shown in Figure 4. It was observed that PMMA increased the strength of the vertebrae not only to the point of failure, but throughout the testing process compared with the intact, negative, and copolymer specimens. The negative group specimens showed a failure strength lower than the intact and copolymer groups, while these two presented similar outcomes.

The ultimate strength for the negative, intact, copolymer, and PMMA groups was 1.5 ± 0.1 MPa, 2.5 ± 0.4 MPa, 2.7 ± 0.3 MPa, and 4.1 ± 0.6 MPa, respectively (Fig. 5A). The P(PF-co-CL)-treated vertebral bodies had significantly higher ($p < 0.05$) strength than the untreated, negative control, and was similar to the intact vertebral body. In contrast, the PMMA-treated group had significantly higher strength ($p < 0.05$) than the intact control.

Due to specimen and vertebral variability, the ultimate strength values were also normalized to vBMD measurements (Fig. 5B). Similar to the unnormalized data, the normalized average ultimate strength/vBMD of the copolymer group was significantly higher ($p < 0.05$) than the negative control, while significantly lower ($p < 0.05$) than the PMMA group.

The elastic moduli of the vertebral bodies followed a similar trend (Fig. 6A). The copolymer group (98.1 ± 14.2 MPa) showed a significantly higher modulus than the negative control (54.2 ± 4.9 MPa, $p < 0.01$), but a significantly lower value compared with the PMMA group (146.3 ± 16.3 MPa, $p < 0.05$). There is no significant difference between the intact control

(90.5 ± 9.9 MPa) and the copolymer group ($p > 0.05$). Same statistical difference was observed with normalized elastic modulus/vBMD data (Fig. 6B).

Discussion

The ideal filling material for vertebroplasty should have compatible biomechanical properties to trabecular bone, high biocompatibility, biodegradability, and *in situ* crosslinkable without local high temperature increase.²⁷ On the basis of these criteria, PMMA is far from ideal although it is widely used clinically.^{28–30} As a result, extensive research has been conducted in recent years to explore more appropriate bioactive materials to substitute PMMA in vertebroplasty.

We have developed a promising new material, P(PF-co-CL), as an injectable scaffold for bone defect repair.¹⁸ We showed

FIG. 3. (A, B) Gross and quantitative computed tomography illustration of the simulated lytic defects filled with either (C, D) PMMA or P(PF-co-CL) (E, F). PMMA, poly(methyl methacrylate). Color images available online at www.liebertpub.com/tea

FIG. 4. Typical load–displacement curves obtained for each experimental group.

the maximum crosslinking temperature of the copolymer to fall between 38°C and 47°C, much lower compared with PMMA. The compressive moduli of P(PF-co-CL) scaffolds ranged from 44 to 142 MPa, similar to human trabecular bone.^{17,18} These results indicate that P(PF-co-CL) may be a promising candidate material to substitute PMMA in vertebral body.

In this study, we evaluated the biomechanical performance of the copolymer in a cadaver model of vertebral lytic lesions. We especially compared the copolymer-augmented vertebral bodies with intact vertebral bodies, untreated defects (negative control), and vertebral bodies with PMMA augmentation. Our results demonstrated that both PMMA and P(PF-co-CL) copolymer were able to significantly increase the mechanical properties of the vertebral bodies with lytic lesions. However, only the polymer group was able to restore both ultimate strength and elastic modulus to its normal values. The PMMA-augmented groups had significantly higher strength and modulus than the normal group. This strength and modulus mismatch between PMMA-treated vertebrae and the host vertebrae could potentially induce fracture in the levels adjacent to the treated segment.

To isolate geometrical differences from individual vertebrae that could have impacted our results, the biomechanical data were normalized to BMD measurements obtained from imaging analysis of the DICOM images from the QCT scans. Ultimate strength/BMD of the copolymer group was again larger than the negative control, and despite presenting smaller values compared with the intact specimens, these two groups showed no statistical difference. In contrast, PMMA significantly increased the strength of the vertebral bodies compared with the intact and copolymer groups. The same trend was observed for the elastic modulus. These results again confirmed that vertebral augmentation using copolymers, but not PMMA, restored vertebral body strength and modulus to levels comparable to normal vertebrae.

Permeation of filling material into the trabecular bone space around the defects can result in a tight mechanical interlocking fixation.^{31,32} In our study, although PMMA also penetrated into the trabecular structure, the copolymer filling covered a larger section of the trabecular microstructure displaying a finger-like pattern between the filling materials and surrounding trabecular bone (Fig. 3). This permeation

FIG. 5. (A) Ultimate strength and (B) ultimate strength/vBMD data. *Represents a significant difference at the 0.05 level. vBMD, volumetric bone mineral density.

FIG. 6. (A) Modulus and (B) modulus/vBMD data. *Represents a significant difference at the 0.05 level.

phenomena displayed by the copolymer filling could have an effect in the load transmission within the sample affecting the mechanical properties of vertebrae. It has been demonstrated in previous studies, where a clear fibrous membrane was visible at the interface between PMMA and cancellous bone suggesting a failure of the filler to form a proper bony fusion within the bone matrix.³³ This observation may offer some insight into why some patients experience recurrence of back pain after PVP and percutaneous kyphoplasty with PMMA.³⁴

Potential limitations with studies using simulated metastatic lesions within vertebral bodies relate to the location of defect as well as creating a consistent defect volume within the specimens.³⁵ The actual lesion usually first locates near the center core of the vertebral body with a destructive progression of the microstructure toward the sides.^{36,37} In this study, the vertebral defect was approached by (1) locating the middle point on the lateral side of the vertebral body and removing the majority of the desired trabecular bone volume from the core; and (2) inserting a vertebroplasty balloon through the lateral hole to precisely expand the lytic defect to the desired volume. We found the percentage of the created defect volumes to be $23.3\% \pm 6.2\%$ as calculated from the QCT images, similar to the targeted value of 25%. No statistical difference in the percentage of vertebral body defect volumes was found between the experimental groups ($p > 0.05$). In addition, vertebrae are by nature subjected to cyclic loads and future *in vivo* studies are needed to provide a better understanding of the effect of loading on the time-dependent properties of the copolymer on augmented vertebral bodies compared with intact vertebral bodies. The *in vivo* animal study should assess the evolution of the mechanical properties of the polymeric biomaterial during degradation and whether there exists a gradual stress transfer from the degenerated polymer to the newly formed bone avoiding any potential stress shielding or undesirable vertebral collapse.

Conclusions

The injectable, biodegradable copolymer P(PF-co-CL) exhibits mechanical properties similar to normal trabecular bone in cadaveric vertebroplasty models. This material may be a suitable alternative for vertebroplasty to treat and

prevent burst fractures of metastatic vertebral bodies. Future work aimed at improving cement filling is necessary for safety and consistent stabilization of the metastatic spine with vertebroplasty *in vivo*.

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Disclosure Statement

The authors have no conflicts of interest.

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