INTRODUCTION

Metastatic spinal cancer requires tumor resection and compensation for the loss of structural integrity. Standard post-operative treatment is through systemic drugs and radiation, and implants for support in the event that tissue failure has already occurred. These spinal tumors present a greater problem due to the relative paucity of effective adjuvant therapies, the extremely high propensity for local recurrence and the loss of spinal stability. We propose a course of study for the development of a tailorable drug delivery method based on transport and diffusion from materials already approved for clinical usage in humans. In this study we examined the drug release from a drug laden composite cement. We hypothesize that the mechanical properties and the permeability of composite bone cements may be controlled through pore structure parameters of a particular composite, thereby allowing the drug release kinetics to be tailored without loss of mechanical integrity.

METHODS

Drug laden bone cements were created from PMMA and doxorubicin. The doxorubicin was mixed with the powdered PMMA (Surgical Simplex, Stryker Corporation, NJ) monomer in a 2.5wt% ratio. Monomer, crosslinker and NaCl porogens were mixed together and packed into HPLC vials. NaCl of side length 500-700um were used as porogens in four quantities: 0, 30, 45 and 60 percent volume with respect to the PMMA. Scaffolds were allowed to fully harden before breaking them out of the glass vial. Scaffolds were then placed in a tube containing 1.0 ml of PBS at 37°C. Vials were stored in the dark to prevent denaturation of the doxorubicin and were rocked for the duration of the experiment.

Release kinetics were measured up to 28 days via absorbance using a spectrophotometer at 530 nm. After each reading, one ml of fresh PBS (at 37°C) was added and the tubes were returned to the rocker in the dark field. Each reading was added temporally to give the cumulative effect. A preliminary study verified the spectrophotometer as a viable tool to correctly measure the doxorubicin concentration in the PBS. Following 28 days the scaffolds were dried and weighed to prepare for morphological analysis and permeability testing. Scaffolds were scanned using micro-computed tomography (μCT) with a methodology described previously. Samples were contoured and morphological measurements were taken to determine porosity, total surface area, surface to volume ratio and degree of anisotropy.

RESULTS

Our findings using PMMA scaffolds revealed an increase in the release when various percentages of salts (500-710 microns) were added. The majority of the drug was released in the first 48 hours of the study, with the remainder of the drug being released cumulatively through the 28 day study. Significance in drug release was seen with the 45% and 60% porous samples but not with the 30% samples. The mean difference between 30% and 0% salt is –0.38 (se = 0.102), the mean difference between 5% and 0% is 0.42 (se=0.112) and the mean difference between 60% and 0% is 1.22 (se=0.135). For the concentration, the time slope is 54.7 μg per day before day 3 and 7.7 units per day after day 3; the mean difference between 30% and 0% salt is 0 (se = 6.7), the mean difference between 45% and 0% is 51 (se=7.4) and the mean difference between 60% and 0% is 112 (se=8.9). These results are based on linear models fit to all 1002 observations. Results of the micro-computed tomography scan showed that the intended porosities of 0.3, 0.45, 0.6, and 0.9 corresponded to actual porosities of 0.03, 0.12, 0.27, and 0.50. PMMA samples which had no salt mixed with them showed air bubbles which raised the porosity above the intended value of 0.0. The low release in these samples was accounted by the fact that the surface to volume ratio of these scaffolds was 2.0 compared to the non-porous samples which had a surface to volume ratio of 1.4. Surface to volume ratios of the 0.45 and 0.60 samples were 10 and 14, respectively.

DISCUSSION

When the structural integrity of bone is compromised due to diseases like cancer, fractures may occur. Current treatments are typically with systemic drugs and radiation, and implants for support in the event that failure has already occurred. There is currently no viable method to create implants with a combination of drug release components. This study demonstrates that the creation of porous drug laden implants is possible and tailorable. CT scans of the 0.30 and 0.50 samples demonstrated that PMMA is impermeable to water in static conditions. Additionally, the μCT scans demonstrate that for a specific porogen there is a threshold below which there is no interconnectivity. Below this low threshold, the drug release is not statistically significant in comparison to the non-porous sample but the mechanical properties are significantly reduced. The next step of this research is to develop an injectable version of these implants for testing in vertebral trabecular bone. Figure 3. illustrates PMMA plus 0.60 volume fraction NaCl, significantly higher than is required for interconnectivity as a result of the bone architecture. Lower required porosities will result in higher mechanical properties of the resulting composite. Following drug release studies with the bone core composites, a regression model describing the interrelationships between pore structure parameters of each composite and their contribution to the permeability and mechanical properties for the composite alone will be constructed.

REFERENCES


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