Monitoring the delivery of therapeutic agents from antibiotic-loaded bone cement with contrast-enhanced MRI

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Introduction: Periprosthetic infection is a devastating complication of joint replacement. Infectious organisms form biofilms on the surface of implants that are highly resistant to antimicrobial therapy. Systemic antimicrobial treatment can kill planktonic bacteria, but is ineffective in treating bacteria in biofilm due to low local concentrations. Traditional local delivery experiments[1] have explored release characteristics of many different local depot devices, including orthopaedic bone cement (poly methyl-methacrylate) *in vitro*.[2,3] There is a considerable disconnect, however, from infinite-sink drug delivery experiments and actual drug distribution in the body. This study has sought to bridge that gap through tracking Gadolinium (Gd) marked small molecules after release from orthopaedic delivery devices. We examined whether MRI[4] could be used to track the delivery of small molecules through the complex delivery environment of bone, local tissues, and local blood flow. If it is possible to characterize the distribution of antibiotics across space and time in complex orthopaedic wounds, better vehicles and therapies can be designed to manage infection in orthopaedic patients.

Method: MRI measurement was performed on a 7T Bruker Biospec small-animal scanner. All scans were acquired with the following parameters: FOV=10cm, matrix=256x256, TE=9.0ms. RARE=4. To test the relationship between the concentration of Gd and T1, agarose hydrogels were prepared with known Gd concentrations. 21 rabbits (body weight = 2kg±0.5kg) were then imaged to study the elution of the drugs in the femur and muscle. Anesthesia was induced with ketamine/xylazine and maintained on 2% isoflurane. 50 slices were acquired with slice thickness=2mm. T1 maps were acquired with a multi-TR RARE sequence, with TR=1058ms, 1500ms, 3000ms, and 5000ms. Axial RARE scans were executed preoperatively as a reference. For most animals, an intramedullary rod was placed percutaneously through a stab wound using a 0.62 Kirschner wire to enter the femoral canal in a retrograde fashion through an entry point in the femoral groove. The entry point was expanded to 3.5 mm with a drill. A 1g Gd-DTPA-impregnated PMMA rod with 10g of xylitol was then placed in the canal. In some animals, a model wound was made in which skin and fascia were incised longitudinally over the anterolateral 2 quarters of the thigh. The quadriceps was split in the direction of muscle fibers down to the femur. Bone was excised to create a 1/3 circumference, 2cm long defect, and the defect was filled with a local delivery vehicle containing Gd. Layers were closed above the defect using suture. After the surgery, a sagittal T1w image (TR=1000ms) was executed on both legs, followed by axial T1 map measurement. The scans ran periodically for the next 6 hours. An exponential fitting of the T1w signal with different TR was used to get T1 maps. Two ROIs were drawn in the muscle close to the canal and the muscle 3.0 centimeters away. The changes of the mean value of T1 in each ROI over time were studied.

Results: Gd concentrations were determined in hydrogel, and T1 shortening was correlated (R=0.9702) with Gd concentration (fig1). The presence of Gadolinium *in vivo* was determined by relative shortening of T1 in local tissue (fig2. B,C). For the *in vivo* study, the elution of the drugs can be seen within 40 minutes after the surgery, as the hypointensity region shown in the T1 map (fig2. B). The hypointensity region grows slowly following the surgery till 6 hours (fig2. C). In the specified region close to the rod, mean value of T1 decreases over time (fig2A. Red), while it remains stable in the normal tissue region (fig2A. Blue).

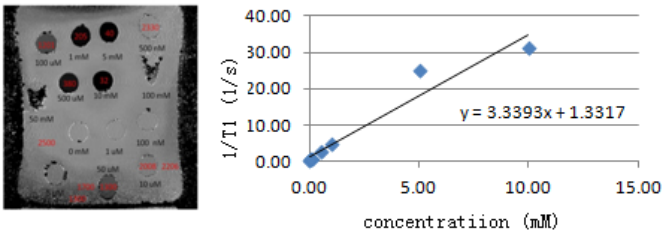

Figure 1. Correlation of T1 with Gd

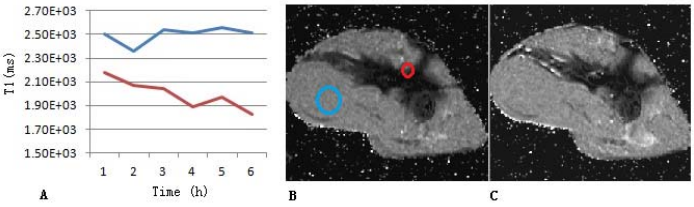

Figure 2. In vivo T1 changes over time

Conclusion: The expanding hypointensity region in T1 maps showed the increased spatial distribution of the drugs over time. The dropping of T1 in the muscle close to the rod indicated the accumulation of contrast agent in that region. The study showed that contrast enhanced MRI is a promising method for the study of orthopaedic drug delivery. Future work will focus on quantification of drug concentrations, and study over longer periods of time. The data gathered in this study will be used to build mathematical models of the distribution of antibiotics in orthopaedic wounds.

Reference: 1) Arlen D. Hanssen et al, Clinical Orthopaedics and Related Research, 2004; 427, 79-85. 2) Alex C. McLaren et al, Clinical Orthopaedics and Related Research, 2009; 467:1693-1698. 3) Kenneth Adams et al, Clinical Orthopaedics and Related Research, 1990; 278: 244-252. 4) Xiaoming Chen et al, Magnetic Resonance Imaging, 2008; 26:1433-1441.