A Novel Method for Intra-Articular Particle Administration in an In Vivo Model of Osteolysis

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Objective/Aim/Hypothesis: Long-term resistance to implant loosening depends upon establishment and maintenance of the bone-implant interface. The primary mechanism of aseptic loosening involves particle-induced peri-implant osteolysis in which debris released from the implant triggers local inflammation, leading to the release of osteoclast-stimulating cytokines and eventually osteolysis [1-10]. Particle-induced osteolysis is a key factor in failure of orthopedic implants [10-12]. In an effort to optimize our *in vivo* rat model of osteolysis, we tested a novel particle delivery method in young and aged rats.

Design/Approach/Methods: Our IACUC approved study included 30 young and aged male Sprague-Dawley rats (n = 15 young, ~4 mo. old, n = 15 aged, ~12 mo. old). All rats underwent bilateral implant surgery to place titanium rods (15mm x 1.5mm) in the femoral intramedullary canal via the knee joint. At surgery, the right knee joints of all rats were administered a custom poly(ethylene) glycol diacrylate (PEGDA) hydrogel that was pre-loaded with either vehicle (6% rat serum) or 9.38×10^9 particles/mL of lipopolysaccharide-doped polyethylene (LPS-PE) particles or 1mg of cobalt chrome alloy (CoCr) particles. Hydrogels were designed with proteolytic sensitivity initiated by a 30 minute soak in a 1μg/ml collagenase solution to ensure complete material degradation and particle release 5 hours post- injection. Beginning the day after surgery, the left knee joints were manually administered either vehicle, LPS-PE or CoCr particles intra-articularly. Intra-articular injections were administered once weekly for 6 weeks. At 6 weeks, rats were sacrificed and bilateral femora were collected and frozen in saline-soaked gauze for micro-computed tomography and mechanical testing. Two-way analysis of variance were completed for intra-articular challenge (vehicle, LPS-PE or CoCr) by age comparisons for manual and hydrogel administration using SPSS (v.19 for Windows, Chicago, IL).

Results: Implant fixation strength was not significantly different between intra-articular challenges when administered by hydrogel ($p = 0.097$), however, there was a significant difference when administered manually ($p = 0.032$). There was a significant age effect for hydrogel administration ($p = 0.027$), but not for the manual administration ($p = 0.086$). Peri-implant bone volume fraction (BV/TV) was moderately significantly different between intra-articular challenges when administered by hydrogel ($p = 0.049$) and trended toward significance for manual administration ($p = 0.058$). BV/TV was significantly decreased with age in hydrogel and manual administration routes ($p < 0.001$). There were no significant interactions for fixation strength or BV/TV.

Conclusion: Surprisingly, our data show that administration of a large bolus of particles near the time of implant surgery did not significantly decrease implant fixation strength or peri-implant BV/TV compared to a gradual, manual administration of particles over 6 weeks. The age of the rat had significant effects on BV/TV, but less on implant fixation strength. Together, this suggests that 1) optimizing our *in vivo* model of osteolysis by administering the full particle dose at surgery does not amplify the inflammatory particle response and that 2) aged rats respond differently to a particle challenge compared to young rats and may be more translational to the human population receiving total joint replacements.

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