Polyvinyl alcohol-polyacrylic acid (PVA-PAA) hydrogels for osteochondral defect repair

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Statement of Purpose: Cartilage injury caused by arthritis is a major cause of disability in the U.S.[1] Once injured, chondrocytes cannot innately heal, resulting in focal cartilage defects that further the progression of osteoarthritis (OA). This leads to the loss of cartilage tissue and often results in costly joint arthroplasty procedures due to limited therapies that restore the articular cartilage to its original uninjured state. The purpose of this study was to (i) assess the biocompatibility of a polyvinyl alcohol-polyacrylic acid (PVA-PAA) hydrogel formulation in a New Zealand white rabbit (NZWR) model, (ii) determine its ability to function as a condylar osteochondral tissue replacement, and (iii) quantify changes in material properties of the hydrogel pre and post implantation over a 12 and 24-week period.

Methods: A PVA-PAA solution at a 19:1 ratio was molded into rods for OCD repair and sheets to template tensile bars to be implanted subcutaneously to determine any potential *in vivo* changes in mechanical properties. Prior to implantation, the rods and sheets were subjected to a freeze-thaw cycle, subsequently immersed in polyethylene glycol (PEG), and annealed in a pressure vessel under air at 160°C. Hydrogels were then rehydrated and sterilized with irradiation of 25 kGy in PEG. After IACUC approval, hydrogels were implanted into a critical size OC defect according to ASTM standards F2451-05 in skeletally mature male NZWR (n=9). The hydrogel rods implanted in a PEG-dehydrated state were expected to equilibrate with the synovial fluid, creating a press fit that would provide fixation. Additionally, hydrogel tensile bars (n=2 per rabbit) were implanted subcutaneously in the dorsum. Euthanasia and sample recovery occurred at 2 weeks (n=1), 12 weeks (n=4), and 24 weeks (n=4). At the time of explantation, synovial fluid was aspirated and analyzed for PVA contents using ultraviolet visible spectroscopy (UV-Vis) in case that hydrogel degradation occurred. The equilibrium water content (EWC) was determined for both hydrogel plugs and tensile bars; bars were displaced at a rate of 20 mm/min using an MTS Insight 2 tester. The medial condyles were subjected to high-resolution micro-computed tomography (micro-CT) analysis to evaluate the interface between the hydrogel and the subchondral bone. The joint capsule, meniscus, and osteochondral tissue was processed for histological analysis and reviewed in a blinded fashion by a senior pathologist at our institution. A study outline is presented in Figure 1.

Results: No adverse post-operative events were encountered and all samples were recovered at the time of explantation. Hydrogel retrieval at 2 weeks confirmed implant location in situ. The 12-week OC implants were flush with the articular surface, and histological analysis revealed intact meniscal and counterface cartilage surfaces. The 24-week OC implants protruded approximately 500 microns from the articular surface, most likely due to excessive rehydration with synovial fluid. The histological slide review, performed by a pathologist, determined hydrogel biocompatibility (Table 1). No PVA particles were found in the synovial capsule and the articular cartilage had a normal appearance. The micro-CT analysis ruled out any formation of bone cysts and osteolysis (Figure 1). Additionally, no PVA contents were found on the synovial fluid analysis via UV-Vis. In regards to the tensile bars implanted in the dorsum, upon explantation they were surrounded by a thin capsule that was easily removed and did not adhere to the hydrogels. No significant changes were found in the break stress, strain at break, modulus, or EWC of the tensile bar-shaped hydrogels between the 12- and 24-week period (Table 2).

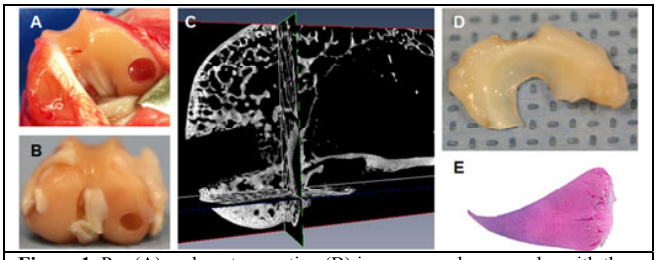

Figure 1. Pre (A) and post-operative (B) images are shown acobe with the PVA-PAA hydrogel rod in place at 12w. The micro-CT imaging (C) demonstrated a normal subchondral bone architecture. Both grossly (D) and histologically (E), no damage was present in the meniscus.

	2w (*n*=1)	12w (*n*=4)	24w (*n*=4)
Capsule surrounding tensile bars	Fibrous connective tissue with blood vessels	Same as 2w	Same as 2w
Synovial capsule	Hyperplastic synovium, no foreign body or giant cell reaction	Same as 2w	Same as 2w
Tibial cartilage	No surface damage	No surface damage	Chondral defect in tibial plateau
Meniscus	Intact, no damage	Intact, no damage	Fibrillation at surface

Table 1. Summary of histological findings at 2, 12 and 24 weeks.

	Break stress (MPa)	Strain at break (%)	Modulus (MPa)	EWC (%)
12w *in vivo* tensile bars	13±1.7	352±29	7±0.66	56±2.1
24w *in vivo* tensile bars	13±1.8	351±32	7±1.9	55±1.8
Tensile bar control (non-implanted)	15±0.44	380±16	9±0.65	48±2.4
12w *in vivo* OC plug	*	*	*	54±2.4
24w *in vivo* OC plug	*	*	*	54±3.6
OC plug control (non-implanted)	*	*	*	48±2.4

Table 2. Summary of hydrogel properties before and after implantation. *=Testing does not apply.

Conclusions: There is an urgent need for a biomaterial that can be used as an osteochondral tissue replacement for isolated lesions to reduce the burden of OA and costly joint arthroplasties. Strong and lubricious PVA hydrogel-based materials are optimal candidates for cartilage tissue replacement, and this study demonstrates feasibility of evaluating this PVA-PAA hydrogel in a swine model.

References: 1. Temenoff JS, Mikos AG. Review: tissue engineering for regeneration of articular cartilage. Biomaterials. 21:431-40. 2000.

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