Preclinical Evaluation of Intrinsically Radiopaque Hydrogels for Replacing the Nucleus Pulposus

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INTRODUCTION: Nucleus replacement is a promising new approach to treat mild cases of degenerative disc diseases. Current prosthesis designs [1-2] have several disadvantages: they are radiolucent, which makes exact positioning within the annulus difficult, and they do not fill the entire cavity, which alters the stress-distribution in the intervertebral disc. Here we describe a new type of prosthesis based on intrinsically radiopaque hydrogels that possess controllable swelling and mechanical properties. To serve as a nucleus replacement, the prosthesis should meet the following requirements: 1)Dry implantation through a small incision in the annulus with subsequent *in situ* swelling to fill the entire nucleus cavity; 2)Excellent visibility with X-ray fluoroscopy and MRI, without artifacts; 3)Adequate mechanical properties and fatigue resistance.
We designed and studied different hydrogels that fulfill these criteria. From one material, a prototype nucleus prosthesis was prepared, which was evaluated in a realistic model.

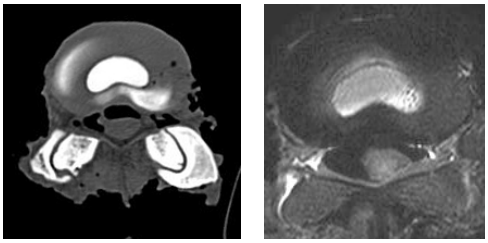
METHODS: Hydrogels were prepared by copolymerizing either N-vinyl pyrrolidinone (NVP) or hydroxyethyl methacrylate with the radiopaque monomer 4-iodobenzoyl-oxo-ethyl methacrylate (4IEMA) [3] in the molar ratio 94/6. The resulting copolymers are indicated by N94 and H94 respectively.
Swelling studies were conducted at room temperature in PBS. Their E-modulus was determined at 37 °C in a water bath. Biocompatibility was verified *in vitro*, using the MTT and Live/Dead assays, and *in vivo*, by subcutaneous implantation in mice. The mice were sacrificed after 1 week and 3 months. PMMA was also implanted as a reference material. A prototype nucleus prosthesis was made from N94 and was implanted into an explanted porcine lumbar spine. It was allowed to swell overnight and visualized using CT and MRI.

RESULTS: Swelling studies showed that N94 absorbs more water than H94, however their E-moduli are comparable (table 1) and within the desired range of 0.2 – 4 MPa [4]. The *in vitro* cytotoxicity assays showed that both materials are non-cytotoxic.

Table 1. Equilibrium water content (EWC) and E-modulus

	EWC	E-modulus
N94	74%	1.4 MPa
H94	23%	1.2 MPa

After one week of implantation in mice there was only a mild acute inflammation. After 3 months a thin fibrous capsule surrounded all implanted materials and macrophages were only sporadically detected. The prototype prosthesis was easily implanted through a small incision in the annulus, which was closed with suture. After overnight swelling, the hydrogel filled the entire cavity and clear CT and MRI scans could be obtained (fig. 1).
Fig. 1: CT scan (left) and MRI scan (right) of N94 prosthesis in a porcine model.



DISCUSSION & CONCLUSIONS: Both N94 and H94 appear to be biocompatible hydrogels. With its high swelling capacity, N94 will be easiest to implant through a minimal incision in the annulus. The prototype implantation proved the suitability of the new nucleus prosthesis and visualization was excellent with both, clinically important, visualization techniques, especially as compared to current designs. Future studies will include fatigue resistance tests and long-term implantation in living animals.

REFERENCES: [1] Klara, Ray (2002) *Spine* **27**:1374-1377. [2] Korge et al. (2002) *Eur Spine J* **11**:S149-S153. [3] Kruft et al. (1996) *Biomaterials* **17**:1803-1812. [4] Fagan et al. (2002) *Proc Inst Mech Eng [H]* **216**:299-314